JANUARY 1951

BULLETIN

OF THE NEW YORK ACADEMY OF MEDICINE

Original Articles

by

DONALD McEACHERN

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1. Zipkin, M. M. Times, New York 78: 205, 1950.
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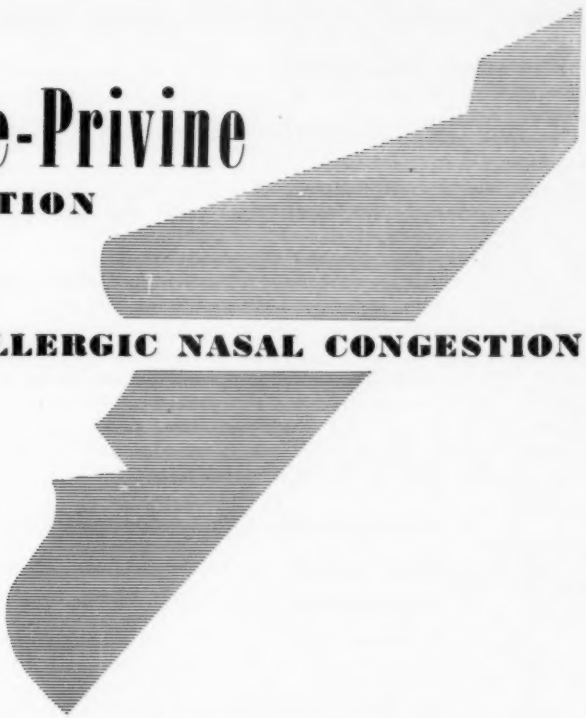

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1. Friedlaender & Friedlaender: Amer. Pract. 2:643, June, 1948

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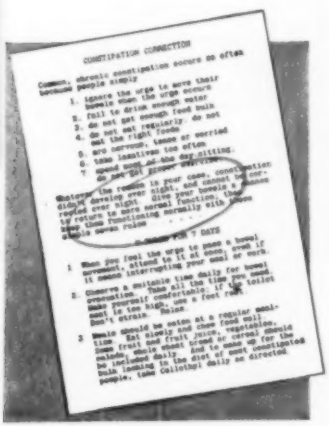
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1. *Bargen, J. A.: Gastroenterology 13:275, 1949.*

2. *Musick, V. H.: J. Oklahoma M. A. 43:360, 1950.*

3. *Schwelg, K.: New York State J. Med. 48:1822, 1948.*

4. *Council on Pharmacy and Chemistry: J.A.M.A. 143:897, 1950.*

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MAHLON ASHFORD, *Editor*

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BULLETIN OF
THE NEW YORK ACADEMY
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VOL. 27, NO. 1 JANUARY 1951

DISEASES AND DISORDERS OF MUSCLE FUNCTION*

DONALD McEACHERN

Chief of Neurological Service, Montreal Neurological Institute

I WOULD like to discuss with you tonight some disorders of muscular function in man. It would not be profitable to deal with all the muscular ailments. I shall deal, therefore, with several prototypes that illustrate the great range and variety of mechanisms that make a man's muscles sick.

Some of these conditions are rare—but let that not dismay you. Addison's disease is rare, but it has led to fantastic discoveries of the role of the adrenal cortex and the glandular chain in health and in disease. In like manner a knowledge of the mechanism of muscular disorders may illuminate many other fields of medicine and may clarify the manifold problems of muscular fatigue.

But let us not quickly divorce the muscle from its bride, the anterior horn cell. They form a unit in health, and also in diseases which we call neuromuscular disorders. Our conception of this unit is shown in Figure 1.

* Given October 10, 1950 before the 23rd Graduate Fortnight of The New York Academy of Medicine. From the Department of Neurology and Neurosurgery, McGill University and the Montreal Neurological Institute.

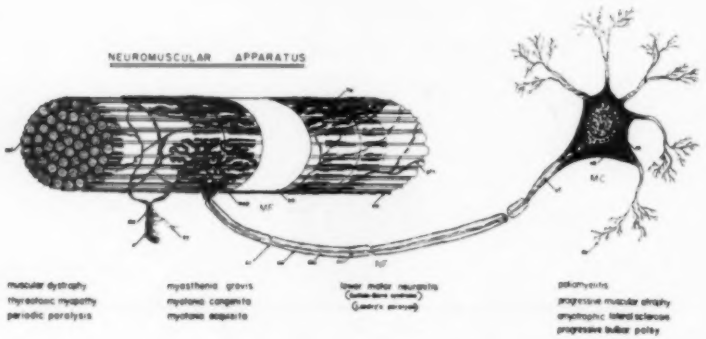

Fig. 1—Diagram of lower motor neurone. Main sites of disturbance in various diseases are shown.

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The term "Neuromuscular Disorders" includes the conditions which affect, in a systematic way, the anterior horn cell, the nerve fiber, the neuromyal junction, or the muscle fiber.[1] We group these together not upon anatomical grounds but because disturbance of one part of the lower motor neurone is apt to involve the other parts. Furthermore, their chemical processes and their vulnerability to noxae are often similar. Diseases quite different in causation may produce similar disturbances of function (e.g., pain, muscle spasm, fasciculation, atrophy). These often require skilled interpretation by specialized methods. Future advances in our understanding and treatment of these conditions must be based upon a knowledge of the physiology and chemistry of the lower motor neurone. Tonight, however, we will deal mostly with disorders of muscle.* You will hear about such strange things as myotonia, myasthenia, thyroidal muscular disorders, periodic paralysis and dystrophies, and I hope that you will find interest in them.

The Myotonias

Myotonia is a symptom. It consists in the prolonged contraction of

* The work to be described has been carried out over some years with the assistance of my colleagues Drs. Robert Pudenz, Guy Odom, Wolfgang Klemperer, William C. Gibson, Reuben Rabinovitch and G. Milton Shy.

a muscle, or a part of a muscle, after cessation of the stimulus–be it voluntary, mechanical or electrical. With a voluntary movement a whole group of muscles may remain in contraction for some seconds before relaxation sets in. A similar but very localized contraction follows stimulation of the muscle by percussion, an electrical shock or the prick of a needle. When a movement is repeated a number of times the muscles "warm up" and normal contraction and relaxation occur. The myotonia returns again after a period of rest. Myotonia may be demonstrable clinically in all the voluntary muscles, or it may be limited to a few, such as the thenar muscles and the tongue. In such cases, however, the more refined method of electromyography sometimes shows that the myotonia is more widespread.

Myotonia occurs with two rare but well recognized diseases–myotonia dystrophica and myotonia congenita. It has been reported also in association with myxoedema or hypothyroidism, and in these instances it responds to treatment with thyroid. It also occurs in goats as an hereditary disease which seems identical to myotonia congenita in humans.

What is the nature of myotonia? This has been a matter of debate for many years. Myotonia persists after blocking of the motor nerve and after spinal anaesthesia, thus indicating a peripheral mechanism. Recent electromyographic work has shown that the abnormality lies predominantly or altogether in the muscle.

Brown and Harvey[2] have studied the mechanism in myotonic goats. Electromyograms show a long-lasting, irregular tetanus. The response of the muscle to a single motor nerve stimulus is repetitive in nature. The myotonic response to mechanical stimulation is not diminished by full curarization, nor by section and degeneration of the motor nerve. Response and threshold to acetylcholine is the same in myotonic and normal muscle, but the response is much prolonged in the myotonic goat.

There are interesting relationships to potassium. Myotonic muscle is abnormally sensitive to the potassium ion. Epinephrine, which lessens the stimulation of striate muscle by potassium, reduces the myotonia of goats and of humans. Desoxycorticosterone, which influences potassium balance and lowers serum potassium, abolishes myotonia in the goat. Both epinephrine and desoxycorticosterone are capable of producing a fall of serum potassium and paralysis in persons subject to periodic paralysis.

Kennedy and Wolf[3] suggested that myotonia and myasthenia gravis were clinical opposites because of their opposite reactions to neostigmine and quinine. They even went so far as to cross-transfuse two patients who had the respective diseases. No improvement occurred in either. The concept is interesting but does not fit all the facts. The supposition that myotonia may be due to increased liberation of ACh at the neuromyal junctions has no proof to support it.

The improvement of myotonia by quinine is due to its ability to suppress repetitive muscle responses of all types, and also to its curarizing action, which diminishes the number of impulses reaching the muscle fiber. Quinine is prescribed clinically for its symptomatic effect in reducing myotonia, and the drug can be given by mouth for this purpose.

We have recently discovered that myotonia is abolished by cortisone. Within four or five days the muscles become normally quick and agile. In one case of myotonia atrophica, for example, the electromyogram showed repetitive volleys lasting for one minute and sixteen seconds after the stimulus. This was reduced to zero on the fifth day of cortisone therapy. The myotonia returns, however, when the hormone is discontinued. Whether or not the underlying muscular defect in myotonia dystrophica can be influenced by cortisone requires further investigation.

Myasthenia Gravis

This extraordinary disease is characterized by weakness and undue fatigability of the skeletal muscles. Heart and visceral musculature is not involved. The patient is apt to have drooping eyelids, a blank, expressionless appearance, a nasal voice, and difficulty in chewing and swallowing. In severe cases there may be weakness and fatigability of the limb muscles so that arms and legs can scarcely be lifted. In extreme cases the respiratory muscles may be affected, and the patient dies of respiratory paralysis or spasm of the larynx. The above features resemble unmistakably the acute and evanescent effect of curare poisoning.

The character of myasthenia gravis is suggestive of an endocrine or metabolic disorder. Onset is usually after puberty and in early life. There is a tendency to remissions. Modifications of the disease may occur during pregnancy or with changes of thyroid function. At autopsy no structural change is found in the nerves or muscles save for the

presence of scattered lymphorrhages, which can scarcely be considered causative. The only other common finding is hyperplasia or tumor formation in the thymus, which occurs in a suggestive number of cases,[4] viz., about 50 per cent of reported autopsies (weighted) and about 10 per cent of surgical explorations in unselected cases. Even the latter figure is high.

There are other similarities too between myasthenia gravis and curare poisoning. Numerous electromyographic studies indicate that in both conditions there is a sort of block to normal neuromuscular function. The motor nerve fibers conduct normally, and the response of muscle to direct stimulation is normal, but the transmitting machinery from motor end-plates to muscle does not function properly. Furthermore, both conditions respond dramatically to anti-cholinesterase drugs such as eserine and neostigmine. The myasthenic patient is made much worse by small doses of curare.

Let us examine the various possible derangements that might occur in the chemical transmitting mechanism from nerve to skeletal muscle. (a) *Deficient synthesis or liberation of acetylcholine at motor end-plates.* This is a popular theory and may well be the correct one, but it is difficult to prove or disprove. The work of Torda and Wolff[5] would suggest that myasthenic serum contains a substance which inhibits the synthesis of acetylcholine. If this is so, it is strange that other cholinergic functions such as sweating, heart rate, visceral activity, etc., are not grossly affected in this disease. This work requires further confirmation. The beneficial effects claimed by one group of workers[6] for administration of acetylcholine and other more stable choline esters to myasthenic patients has not been confirmed by our own experience. Further critical experiments with newer techniques may give the answer to this important question. (b) *Increased breakdown of acetylcholine due to overactivity of the enzyme cholinesterase.* It has been shown by a number of workers that blood cholinesterase is normal in myasthenia gravis.[7] Muscle cholinesterase has also been found normal in the few cases where the determination has been made. (c) *Diminished sensitivity of muscle to acetylcholine.* Here we run into the confusing observation that myasthenic muscle, unlike curarized muscle, is actually hypersensitive to acetylcholine injected into the nutrient artery.[8] This could mean, of course, that the two conditions are quite different in mechanism. On the other hand, curare poisoning is an acute affair whereas

myasthenia gravis is chronic. We know that denervation of a muscle results, after a couple of weeks, in increased sensitivity of the muscle to acetylcholine. Could it be possible that in myasthenia gravis some long-acting, curare-like substance produces a chemical denervation, with resulting sensitization of muscle to acetylcholine? No answer is at hand on this score. (d) *Presence of curare-like barrier at the neuromyal junction.* It has been reported that release of the tourniquet from an exercised limb in a myasthenic patient causes weakness of relatively unaffected muscles elsewhere in the body.[9] The suggestion is that some curare-like substance has been released from the exercised muscle into the general circulation. These experiments are inconclusive, and in any event might point only to the release of normal metabolites with momentary effect on muscles elsewhere. It is tempting, too, to think of the thymus as perhaps elaborating some curare-like substance with resulting effect on the musculature throughout the body.

We have carried out a large number of experiments along this line.[4] Extracts were made of large quantities of urine from nine patients with myasthenia gravis. These extracts were tested according to the classic frog method of Claude Bernard, and upon the cat's nerve-muscle preparation described by Briscoe. In only one instance could any curare-like effect be demonstrated. Similarly, experiments with defibrinated arterial and venous blood from myasthenic patients were negative. We have also had the opportunity of making extracts of two thymic tumors immediately after their removal by Eldridge Campbell from two patients with myasthenia gravis. No curariform activity could be demonstrated. It is always possible, of course, that these negative results might be due to improper methods of extraction or that the hypothetical curare-like substance might take effect slowly in terms of days or weeks as does, for example, the thyroid hormone. The rate of improvement of myasthenia gravis after thymectomy would tend to support this view. There is as yet, however, no experimental evidence that the thymus has a curare-like function, and the nearest clinical evidence consists in the somewhat encouraging results of thymectomy.

Thymectomy was first embarked upon in an organized way by Blalock of Johns Hopkins Hospital, and it has now been carried out by various surgeons in several hundreds of cases. Keynes has himself completed over one hundred thymectomies.[10] He has summed up his results with the first hundred cases (1942-1947) as follows:

Patients assessed	63
Patients untraced	1
Patients recent	18
Patients died post-operatively	8
Patients with thymic tumors	10
	100

Only one of the patients with thymic tumor showed improvement, and five had died by the end of the third post-operative month. These results are odd. In the sixty-three non-tumor patients whom Keynes assessed the results were as follows:

Assessment	*No.*	*Per Cent*
A. Well, No neostigmine	24	63
B. Almost well	16	
C. Better	18	29
D. No change	5	8

The Mayo Clinic experience has been summarized by Eaton.[11] He analysed results in fifty-two operated cases, of whom twenty had thymic tumors and thirty-two had no tumors. Results were compared with 128 control cases seen in the same period of time. All cases were studied for one year or longer before the evaluation was made. There were 8 per cent remissions in each group. However, 50 per cent of the operated group had shown unequivocal improvement while only 25 per cent of the control group had shown similar improvement.

Harvey[12] has reviewed the experience with 125 cases of myasthenia gravis at Johns Hopkins Hospital, of which thirty-two patients underwent thymectomy. His studies indicate that beneficial results are greater than might be expected from spontaneous remission.

It can only be said that in an encouraging number of cases there has been improvement, amounting in some instances to cure. The disturbing fact remains, however, that some patients are benefited little, and others not at all. This is hard to reconcile with the view that the thymus is primarily responsible.

Let our thoughts remain free, however. Let us reverse the field. What if the thymus is not producing a curarizing agent, but instead is becoming hyperplastic and forming adenomas in response to some need

—a need, perhaps, for increased synthesis of acetylcholine. This might explain Keynes' poor results after the removal of thymic tumors.

In this regard the occurrence of myasthenia gravis in a new-born baby is intriguing. We have studied a young woman with myasthenia gravis of several years' duration. Her thymus had been removed without benefit. Recently she was delivered of a child who had unmistakable signs of the same disease and who responded at once, and was kept alive by neostigmine.* We waited with bated breath to see whether the child's myasthenia would wear off. This it did by the thirty-fifth day, and neostigmine was no longer necessary. For two weeks the child swung in the opposite direction and became hypertonic. It then returned to a perfectly normal state. The mother died on the thirty-fifth post-partum day, apparently due to an increase of her myasthenia. What happened here? Did the mother pass some curarizing substance across the placenta to her child, or did she drain some precursor of acetylcholine from the child? Who knows?

Both ACTH,[5] and cortisone appear to make the myasthenic patient worse during the period of administration. In the case depicted in Figure 2 cortisone had to be stopped on the fifth day due to severe increase of symptoms. This may be important in terms of mechanism. The adrenal cortical steroids have the effect of shrinking the thymus.

Thyroidal Neuromuscular Disorders

Hyperthyroidism. Muscular weakness and fatigability may be prominent in uncomplicated hyperthyroidism. The mechanism is not clear but it seems likely that there is direct embarrassment of muscle metabolism. Certainly creatinuria is marked, and muscle isolated from a hyperthyroid animal uses much more oxygen than normal.[13] In addition, however, there are a number of well-defined neuromuscular disorders which may co-exist with hyperthyroidism and which may be modified by it. A study of the inter-relationships between these conditions might well shed light upon them or upon the problems of muscular fatigue in man.

The following neuromuscular disorders which may appear with the hyperthyroid state are described briefly in order to emphasize the wide variety of mechanisms that may be involved:

* Geddes, A. K. and Kidd, H. M. Myasthenia syndrome of the newborn, *Canad. M.A.J.* to be published.

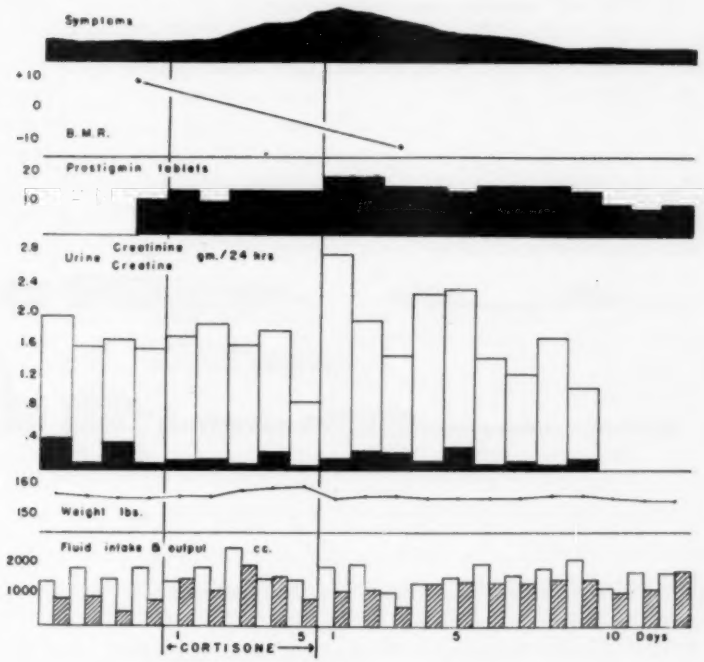

Figure 2—Effect of Cortisone in a case of myasthenia gravis.

(a) *Exophthalmic Ophthalmoplegia.* This consists in progressive protrusion of the eyeballs due to a dystrophic process affecting the extra-ocular muscles. There is edema, fatty infiltration and swelling of the muscle fibers. The condition is apt to appear, or to become aggravated, when the hyperthyroidism is brought under control. For this reason, and because of numerous experimental facts, the anterior pituitary thyrotropic hormone is suspect rather than the thyroid itself. No satisfactory medical treatment has been developed, and surgical decompression of the orbit may be necessary to preserve vision.

(b) *Acute Thyrotoxic Encephalomyopathy.* This jawbreaker title covers fairly completely a condition recently described in the Scandinavian literature. It results in a picture of bulbar palsy sometimes asso-

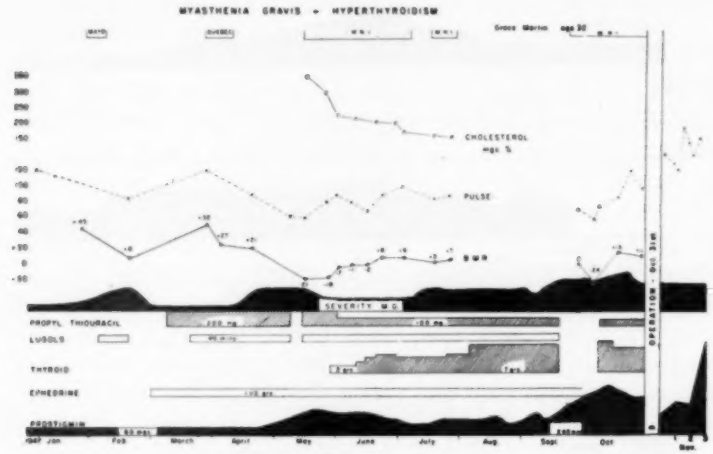

Figure 3—The inverse relationship between symptoms of myasthenia gravis and hyperthyroidism.

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ciated with Parkinson-like tremors and delirium or coma. It is relieved by treatment of the hyperthyroidism.

(c) *Chronic Thyrotoxic Myopathy* is characterized by generalized weakness, wasting and fasciculation of the voluntary muscles. This picture, which resembles so closely the incurable progressive muscular atrophy, vanishes after subtotal thyroidectomy.[14] The condition is apt to occur in older people and without the usual florid evidences of hyperthyroidism such as goiter, exophthalmos or tachycardia.

(d) *Periodic Paralysis.* This condition is really a disorder of potassium metabolism in relation to neuromuscular function. Recurrent attacks of flaccid paralysis occur, lasting many hours and disappearing spontaneously. Attacks are associated with a fall of serum potassium and are rapidly terminated by administration of potassium salts. These bouts of paralysis are greatly increased in frequency and severity in the presence of hyperthyroidism or with thyroid feeding. In Shinosaki's[15] series of twenty-four cases, seven had hyperthyroidism and eight simple goiter. In Tsuji's[16] group of fourteen cases, eleven showed evidence of hyperthyroidism. Whether the so-called Basedow's para-

plegia described in the European literature represents the same thing is not clear.

(e) *Myasthenia Gravis.* The association of hyperthyroidism with myasthenia gravis has been reported rarely. We have assembled data from eight cases, including two of our own.[17]

Of the four instances in which myasthenia gravis appeared before the hyperthyroidism, the later appearance of hyperthyroidism brought unmistakable improvement of the symptoms of myasthenia. There seems to be an inverse, "see-saw" relationship between the two conditions—the myasthenia waning with the onset of hyperthyroidism or waxing with the treatment of the hyperthyroidism. This relationship was observed in both of our cases and was illustrated on five occasions in our second case, as shown in Figure 3.

Hypothyroidism. Myotonia has been repeatedly described both in cretin infants and in adults following thyroidectomy. The symptom is relieved by thyroid administration.

Progressive Muscular Dystrophy

In this condition the muscle fibers undergo slow degeneration with ultimate replacement by fat and fibrous tissue. The trunk, girdle and proximal limb muscles are mainly involved, while the distal muscles of hands and feet are relatively spared. Males are affected about five times as often as females. There is a strong tendency to familial involvement but many sporadic cases are seen.

In the past innumerable groupings have been made (e.g., fascio-scapulo-humeral, pseudohypertrophic, etc.) according to differences in the location of the wasting and age of onset. It does not seen profitable to perpetuate these nosologic refinements unless it can be shown that the groups differ from one another in the cause or mechanism of dystrophy. With our present knowledge the essential process appears to be similar in all, with an exception which we shall describe in a moment.

From the pathological viewpoint the process is confined to the muscles, and changes are not found in the other organs. In the early stages patchy degeneration appears, one affected fiber lying next to several normal ones. The combination of normal fibers with abnormal fibers in various stages of degeneration, down to actual fibrous or fatty replacement, is characteristic.

In sections made from muscle biopsies from our dystrophic patients marked changes in vascular patterns have been found. This is particularly noticeable in the fresh-teased preparations stained by gold chloride. The capillary anastomotic network is denser and more profuse than normal. Arterioles show thickening and proliferation of the medial coat and adventitia. Sometimes complete obliteration of the lumen is observed. It is not possible to say whether these vascular changes are primary or secondary to changes in the muscle fibers. We suspect that they are secondary.

It is of interest that Holman and Swanton[18] produced degenerative lesions in the arteries of young dogs by a combination of renal injury and a deficient diet. It was found that addition of mixed natural tocopherols to the diet prevented the experimental necrotizing arteritis from appearing.

From the biochemical viewpoint, creatinuria is the most characteristic finding. Normally creatine output is about one-tenth that of creatinine in the normal adult male on a meat-free diet. It increases whenever there is a marked degree of muscle breakdown or wasting, from any cause, or with certain metabolic disorders. Creatinuria therefore serves as an index of the degree or nature of muscle involvement.

Hoagland and his co-workers,[19] who have taken up the study some thirty-five years after the original discovery of creatinuria in progressive muscular dystrophy, consider it to be one of the most striking manifestations of the disease. More important is the diminished excretion of creatinine, which provides an even better indication of the severity of the disease than does creatinuria. In muscular dystrophy creatine tolerance is impaired and most of a dose of 1 to 3 Gm. of creatine fed by mouth is excreted in the urine. A normal individual would store all this creatine in the muscles and excrete none in the urine. It cannot yet be said whether the disturbance of creatine metabolism is merely an echo of muscle destruction or whether it plays a more primary and causative role. To some, creatinuria is to dystrophy what glycosuria is to diabetes.

The discovery that vitamin E deficiency in animals caused a form of muscle dystrophy, and that this could be prevented by wheat germ or tocopherols, led to great hopes.

From the beginning attempts were made by clinicians to discover the neuromuscular disease, in man, which might be the counterpart of

TABLE I

Wheat Germ Oil		*Improved*
Juvenile Muscular Dystrophy	25	5
Menopausal Myopathy	5	3
Dermatomyositis	3	3
Unclassified Muscular Atrophy	2	2
Progressive Muscular Atrophy	11	0
Amyotrophic Lateral Sclerosis	14	0
Myasthenia Gravis	11	0
Miscellaneous	36	0
Total	107	

nutritional muscular dystrophy in animals. Therapeutic experiments were undertaken, but some of the early reports of improvement of muscular dystrophy and of amyotrophic lateral sclerosis were over-exuberant and uncritical. Numerous workers have now published negative results in muscle dystrophy and amyotrophic lateral sclerosis.

We present our own experience since it seems to be the most extensive recorded and covers 107 patients with various neuromuscular diseases, some of whom have been under study since 1936.

Wheat germ oil, Milhorat fraction of wheat germ oil, and synthetic alphatocopherol have been used alone and in combination, and in doses as high as 300 mg. daily when computed in terms of alphatocopherol, although the average was less than this, approximating 60 mg. daily. As can be seen in Table I, of a total of 107 patients treated with wheat germ oil, no beneficial effects were observed in amyotrophic lateral sclerosis, myasthenia gravis, disseminated sclerosis and a number of other conditions.

There were thirteen patients in the series who, in our judgement, showed sufficiently striking improvement to warrant the conclusion that treatment was responsible. Two cases of atypical muscular atrophy and five cases of progressive muscular dystrophy (three pseudohypertrophic type and two adult type) showed improvement of symptoms. The two atypical muscular atrophy cases were adult women who had suffered motor neurone disease in early life with a later exacerbation at the involutional period. These are difficult to classify. Three of the

above patients underwent relapse upon discontinuing treatment and improved again when it was resumed. Three other cases, all of whom improved, were labeled as dermatomyositis and exhibited a rubbery kind of dystrophic process in the muscle along with scleroderma-like changes in the skin. Milhorat *et al.*[20] have described two cases of dermatomyositis improved by fresh wheat germ. Our remaining five patients, women at about the climacteric age, exhibited a proximal type of muscle weakness involving mostly shoulder and pelvic girdle muscles. Three recovered almost completely. We have called this menopausal muscular dystrophy. From our experience it is impossible to say whether alphatocopherol or other factors in wheat germ oil were responsible for the improvement, since wheat germ oil, sometimes supplemented by alphatocopherol, was used in all these successful instances.

There are difficulties in establishing a human counterpart to the neuromuscular disorder seen in animals with vitamin E deficiency. A similar disease in man might be chronic and might not respond dramatically to treatment. Further, one would have to postulate some fault of digestion or absorption of the vitamin, since many of these patients take a normal diet. It is of interest that vitamin E is relatively ineffectual when given parenterally to animals with nutritional muscular dystrophy. Recovery occurs, however, when tocopherol is given by mouth, indicating that the vitamin is conjugated or changed in some way during digestion to form the antidystrophic principle. Finally, there is a regrettable confusion in clinical reports as to whether pure alphatocopherol, mixed tocopherols, whole wheat germ, wheat germ oil or one of its fractions has been used. These substances are all lumped together as "vitamin E", whereas some of them contain little of it and others contain a variety of other substances that might be effective.

Wheat germ, so essential to the normal growth of the cereal, is entirely milled off in the making of flour—a situation analogous perhaps to the disappearance of B complex factors with the bran during the polishing of rice. One cannot help but feel that there may be a large and undiscovered territory for the use of wheat germ and its fractions in nutritional and perhaps in hormonal disease.

Periodic Paralysis

(a) *Familial Periodic Paralysis.* This rare disease is characterized by attacks of flaccid paralysis affecting mainly the muscles of the trunk

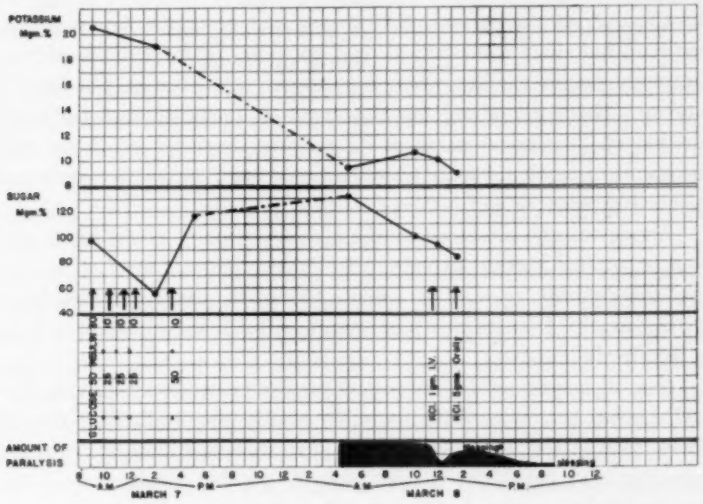

Figure 4—An attack of periodic paralysis induced by glucose and insulin.

(Reproduced from the Journal of the American Medical Association, III, 2253, 1938 by permission of The Journal of the American Medical Association.

and limbs. The deep reflexes often disappear and the muscles become inexcitable to electrical stimulation. Attacks usually come on during sleep, and they last from a few hours to three or four days. In the intervals, muscular power is normal and the patient is entirely well. Attacks first make their appearance during childhood or adolescence and become less frequent, or disappear, in later life. Many theories have been advanced to explain these weird and crippling seizures.

The most comprehensive study of the disease has been made by Shinosaki[15] who published his observations in twenty-four cases. Among the more important observations were the frequent (62 per cent) association of the disease with thyroid struma and the tendency for attacks to occur after administration of thyroid, epinephrine or diets high in carbohydrate. Hyperglycemia was often observed during the early stages of spontaneous attacks.

After some preliminary leads, a number of workers including ourselves pinned the condition down to a fault of potassium metabolism.[21-23]

Attacks of paralysis are associated with a drop of the serum potassium level from the normal of 18-22 mg. per cent to as low as 5 mg. per cent, but there is no critical level for onset of muscular weakness. Recovery occurs rapidly when a potassium salt is given in adequate amount. There is nothing more dramatic in medicine, and the usual hoodoo of "hysterical paralysis" is quickly dissolved when the real mechanism is known. Figure 4 shows the events in an attack which was induced by glucose and insulin.

Attacks can be produced by the administration of epinephrine, glucose or adrenal cortical extract. All of these methods seem to involve the carbohydrate cycle. There is no diuresis of potassium prior to or during attacks. It seems that potassium is called from the blood to meet a need in the muscles.

Not all people with a low blood potassium develop paralysis. It is well known that some diabetics under insulin-glucose therapy show a sharp drop in serum potassium. Muscular weakness develops in some, however, and potassium is now included in the armamentarium for treating diabetic coma. In other words, some patients in diabetic coma are suffering too from periodic paralysis. Overtreatment of Addison's disease with D.C.A. (desoxycorticosterone acetate) may also cause a fall in serum potassium. We have seen several cases with no paralysis despite a serum potassium level below 10 mg. per cent. Ferrebee *et al.*[22] described the equivalent of periodic paralysis in dogs subjected to large doses of D.C.A. In essence, there may be some fault of muscle metabolism too in those who develop profound paralysis with the fall in blood potassium. Several patients subject to periodic paralysis have shown persistent creatinuria in between attacks.

Hubert Jantz,[24] in a study of nine cases of periodic paralysis, found that between attacks all of the serum potassium was ultrafiltrable but during the paralysis only a portion, sometimes less than half, was found in the ultrafiltrate. The potassium concentration of muscle, taken by biopsy during the height of a severe attack, was 710 mg. per 100 Gm. Another muscle sample taken from the same patient 30 minutes after recovery contained 360 mg. per 100 Gm. It seems that skeletal muscle, under some circumstances, has a need for more potassium and that it then drains the blood of its supply. This mechanism must surely operate to some extent in health, and perhaps in a wide variety of metabolic states that lead to minor fatigue and weakness. Jantz thinks that lack

of ionized potassium inhibits the normal cleavage of creatine phosphate in muscle. If correct, this would do more to explain the mystery of periodic paralysis than anything yet.

(b) *Sporadic Periodic Paralysis.* We think that this occurs quite often, but is hard to prove. One patient with no familial history had definite attacks of periodic paralysis. Some mornings weakness of the limb muscles was so great that he could not put on his coat or shave unassisted. Serum analysis at the time of weakness showed a low potassium level (13 mg. per cent) and this returned to normal, and muscle power too, after administration of potassium chloride by mouth. An interesting finding grew out of this. The patient had learned by experience that going out "with the boys for a beer" the night before prevented any muscular weakness from appearing the next day. A request for information from the Black Horse Brewery showed that one quart of the favorite ale contained the equivalent of one gram of potassium chloride. This is not a plug for Canadian ale, for I understand that American brands are equally able to cure certain kinds of paralysis. All beer is high in potassium and, for those of you interested in treating diabetes, orange juice is too.

We have examined two girls in their early teens, each of whom suffered rapid onset of generalized muscular paralysis within a few hours. Both had recovered at the time of the examination, 24 to 48 hours later. In each instance no residual sign of central nervous system defect could be found. We suspect these were isolated episodes of periodic paralysis. Both young women developed symptoms following exposure to cold, and both at the time of a menstrual period. Shinosaki showed that exposure to cold led to attacks of periodic paralysis in some of his cases. Minor instances of periodic paralysis should be sought for in many metabolic upsets where asthenia, stiffness and aching of muscles are a transitory complaint.

Harvey[12] has pointed out that both hypo-potassemia, as shown above, and hyper-potassemia, as met with in some cases of renal failure, may cause muscular weakness and dysfunction, and that a guide to proper therapy may lie in the T wave change of the electrocardiogram which is a sensitive indication of the serum potassium level. Even with the rapid method of determining serum potassium by the flame-photometer, the time lag is too long in these urgent cases and the electrocardiogram is the best running guide.

As shown before, attacks of paralysis can be readily induced in the patient subject to periodic paralysis. One of the simplest means is to administer successive doses of glucose and insulin. This led to the suspicion that some patients being vigorously treated for diabetic acidosis might develop hypo-potassemia. The suspicion proved true. As shown in an excellent exhibit in the Academy tonight, about 20 per cent of such patients develop hypo-potassemia of sufficient degree to cause symptoms or signs.

Nadler and his associates[25] administered potassium to forty-nine patients with hypo-potassemia; twenty-five were undergoing treatment for diabetic acidosis, and twenty-four had intestinal obstruction associated with prolonged vomiting. The potassium deficit was further increased since many of these patients received parenteral fluids from which potassium was omitted. Three of the diabetic patients showed skeletal muscle flaccidity, lowered blood pressure, bounding pulse and a loud systolic murmur. The other patients showed only minor degrees of these manifestations, the most prominent of which were skeletal muscle weakness and/or a decrease in the blood pressure, particularly the diastolic component. Determination of serum potassium was made by the flame photometer. Although the chemical method is of value it was not always practical for repeated determinations. Therefore serial electrocardiograms were made. Prolongation of the Q-T interval with widening of the T wave and lowering or inversion of the T wave (CR_3) were used to estimate the serum potassium concentration.

There is an indication, too, that some patients undergoing insulin shock therapy, who do not recover consciousness when glucose is given, may be suffering from hypo-potassemia. They may recover when potassium is administered.

Hypo-potassemia, then, is a mechanism which may operate in many conditions. We should thank the dramatic grandmother–periodic paralysis, for drawing our attention to it, and we should start to look for the grandchildren who will now begin to make their appearance in many fields of medicine.

Menopausal Muscular Dystrophy

And now, in conclusion, I would like to direct your attention to a form of muscle dystrophy that occurs in later life and which we have named Menopausal Muscular Dystrophy. I have described how three

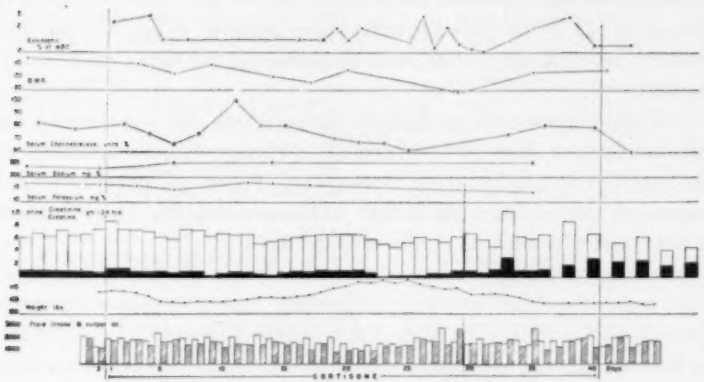

Figure 5—Menopausal muscular dystrophy treated with Cortisone. Creatinuria is not a feature.

out of five earlier cases responded to wheat germ oil therapy. We now find, however, that the response to cortisone can be much more rapid and dramatic, and that the hormone may spell the difference between invalidism and useful activity for these people.

This dystrophy appears gradually, or sometimes rapidly, in the late forty's or thereafter. Women are usually affected, but we have had two men with the condition. There is symmetrical weakness of the girdle muscles, especially those of the hip girdle. This results in the three most characteristic symptoms of the disease: a) inability to rise from a chair unassisted, b) difficulty in climbing stairs, and c) a tendency to unpredictable falls. Since there is no evident wasting, and since deep reflexes are usually intact, the condition is apt to go unrecognized or to be attributed to the enfeeblement of age. Marked creatinuria is not a feature in these cases and it has been a source of disappointment to us that successful treatment with cortisone has not led to any appreciable change in creatine or creatinine output (Fig. 5).

Patients with this condition may respond dramatically to cortisone. Beginning about the fifth day after institution of treatment there is a feeling of increased strength and a perceptible increase in muscle power. One patient on admission, for instance, could climb only five steps in 20 seconds by pulling herself up the railing. After eighteen days of

cortisone therapy she could climb forty steps in the same time without the use of her hands. Other manifestations improve in like manner, and patients may get out and do their shopping for the first time in many months.

At the present time we have six patients with this trouble who are on maintenance doses of cortisone. The average amount necessary to hold them is 75-150 mg. three times a week. When you begin to economize with the cortisone the patient will soon complain. This substance is as necessary to them as insulin is to the diabetic.

We have met with no serious complications in the use of cortisone. The dosage has been usually 100 mg. daily during an active treatment period of up to thirty-five days. A skin eruption appeared in one patient. A lowered glucose tolerance occurred in all, but no glycosuria was met with. No psychoses appeared, and not one out of a consecutive series of sixteen patients showed any change in the E.E.G. This is different from the finding of Hoefer and Glaser with ACTH. The latter substance, of course, calls out many other adrenal hormones in addition to cortisone.

The pathological change in menopausal dystrophy consists in a spotty degeneration and sometimes necrosis, with nearby muscle fibers perhaps unaffected. There may be an increase of sarcolemmal nuclei. In chronic lesions the blood vessels may be thickened, but in general the interstitial reaction is not great. It may be of interest, since we are considering possible mechanisms tonight, that the above picture resembles closely that described by Pappenheimer and others[26] in animals suffering from vitamin E deficiency.

And now, in closing, may I thank you for your attention. May I also express with you the hope that a further knowledge of these mechanisms may soon lead to practical relief for the many who suffer from disorders of muscle function.

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METABOLISM OF CALCIUM AND PHOSPHORUS IN BONE*

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CALCIUM metabolism and bone physiology may well be viewed together since more than 99 per cent of the total calcium content of the body resides in the bones and teeth.[1] The skeleton is a living and not an inert tissue. New bone is constantly being formed and bone is ever being resorbed, not necessarily at the same rates in all bones or even in any one area of a given bone. This has long been known to the pathologist who sees deposition of new bone along one side of a trabecula and its removal on the other side.[2] Since so small a percentage of calcium resides outside the bones, it should be a simple matter to determine whether more bone is being laid down than is being resorbed by observing the calcium *balance*–i.e., if more calcium is going into the body than is coming out, then bone mass must be increasing and vice versa. In general this is true, but such an overall balance will not disclose *where* the new bone is being laid down, and one part of the skeleton might be very active in osteogenesis, another very active in osteolysis, and the sum of the two would equalize. Furthermore, balance experiments are difficult to carry out, and caution must be observed in the interpretation of short-term experiments, for considerable quantities of both calcium and phosphorus (up to several grams) may lie in the gut, presumably in an inert state; especially is this precaution necessary after large changes in the calcium content of the diet[3] or when peristalsis suddenly slows to a point of cessation of stools as in total intravenous feeding.[4]

Although 80 to 90 per cent of the total phosphorus of the body resides in the bones,[5] phosphorus balance is not an accurate gauge of skeletal metabolism, since phosphorus is so widely dispersed and participates in so many complex reactions in all of the tissues of the body. The ratio of phosphorus to calcium of normal bone is extraordinarily

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constant, approximately 2.1 grams of calcium to each 1 gram of phosphorus.[6] However, certain diseases—e.g., rickets—may alter this ratio, phosphate being lower and carbonate higher than in normal bone.[6]

Other things being equal, the size and weight of a bone is dependent on the amount of exercise of the part. The bones of a lumberman are far bulkier and more radiopaque than those of a sedentary office worker. This dependence of size upon activity is readily demonstrable in the atrophy which follows immobilization of a part in a cast. It is remarkable to see the difference in the x-ray appearance of two legs after one of them has been in a cast for a month. Stress of muscular pull and other strains are supposed to play a role in stimulating new bone growth, as exemplified by the obvious efforts of softened and distorted bones to straighten themselves; new bone being laid down much faster on the concave side as compared with the convex. Interruption of the nerve supply to a limb also causes rapid atrophy of disuse, and this is readily demonstrable in patients after poliomyelitis.[2]

The state of the circulation appears to have a profound influence on bone growth. It seems logical that reduction in blood supply should cause atrophy of bone just as it does with other tissues. This concept was utilized by Harris when he performed sympathectomy on limbs which had grown less well as the result of poliomyelitis; he noted increased growth following the procedure.[7] The observation of Pearse and Morton[8] that retardation of the venous circulation enhances bone growth and speeds fracture healing has never been satisfactorily explained. Hypertrophic pulmonary osteoarthropathy exhibits periosteal hyperplasia, which suggests a relationship between O_2 tension or CO_2 tension and osteoblastic proliferation.

Calcium Transport. In order for the constant turnover to take place in bone, calcium and phosphorus must be provided and carried away. This transit is accomplished by the blood stream, extracellular fluids and lymph; but the mechanism of transport of calcium deserves some exposition, since there are wide gaps in our knowledge.

Calcium is present in the normal serum in a concentration of approximately 10 mg. per 100 cc., the range of normalcy usually being considered 9.5 to 11.5 mg. About one-half of this calcium is freely diffusible. McLean and Hastings[9] found by biological assay on the isolated frog heart that nearly all of this diffusible calcium is ionized and only 0.5 mg. or so is in the form of calcium citrate which is dif-

fusible but not electrically charged. The remaining half, or 5.0 mg., is bound to proteins of the serum and presumably does not get beyond the capillary walls in any quantity except when capillary permeability is altered. Although methods for determination of *total* calcium in biological fluids are simple and accurate, estimation of ionized calcium is as yet too complex and laborious for clinical use, and availability of the extracellular fluid for analysis is unusual, to say the least. Thus one knows little about the quantity and state of calcium actually bathing the skeletal tissues except by indirect inference from the total serum calcium and the total serum protein,[9] a decidedly unsatisfactory situation for the clinician and student of bone physiology, as will be pointed out later in discussing hypercalcemic states.

Calcium Homeostasis. As to the *total* serum calcium concentration, it is known that extraordinary control is exerted by homeostatic mechanisms of a very delicate nature,[9] and presumably these same mechanisms exert equal precision over the diffusible and ionized fractions. Some of the factors influencing the total serum calcium concentration may be briefly described.

On minimal calcium diets the balance is negative,[10] and in total starvation calcium continues to be discharged in the urine and feces,[11, 12] the latter probably derived from calcium secreted with the digestive juices and not reabsorbed. Serum calcium concentration does fall after prolonged low calcium intake[13] and under the influence of certain ion exchange resins[14] which, when added to the diet, block absorption of calcium as well as other cations. Since there is only about 1 gram of calcium in the total body fluids, under any of these circumstances of depletion, the serum calcium would fall *rapidly*, unless calcium were supplied from some source; and the only available source is the bones. It is obvious that the skeletal calcium is usually available for maintenance of the serum concentration. But the mechanisms for rendering skeletal calcium available for serum homeostasis are obscure, and in disease states involving diarrheas and especially steatorrheas, one sees patients with low serum calcium and tetany early in the process before x-ray evidence of decalcification exists, but in some patients with the most radiolucent skeletons the calcium of the serum remains normal.[15]

Little is known about calcium absorption from the gut; in what state it crosses the mucosal membrane to gain access to the circulation and the quantitative aspects of the absorptive process are obscure. There is

evidence that most calcium is absorbed from the upper intestinal tract, that acidity favors absorption, and that the amount absorbed bears an inverse relationship to certain other substances present for which calcium has a relative affinity.[16] The difficulties of interpreting balance data because of variabilities in rate of calcium and phosphorus movement along the fecal column have been mentioned. In a normal adult individual, calcium equilibrium may be assumed; and, hence, the daily amount absorbed from the gut will be reasonably accurately reflected by the urinary content of calcium. Normal persons do not excrete more than 250 mg. of calcium per day in the urine, even though they may drink a quart or more of milk per day. The evidence seems to point strongly that only small amounts of calcium are usually absorbed; Albright has guessed 100 mg. per day.[17]

Other factors than the acidity of the medium and the coincident ingestion of calcium precipitating agents, such as oxalate and phosphate,[16] also influence calcium absorption. Vitamin D seems a necessary factor for optimal absorption. In vitamin D deficiency the absorption of calcium is very low; and on administration of vitamin D, one of the first detectable changes is that the absorption rises.[18, 19]

Any diarrhea of magnitude is accompanied by excessive calcium in the stools and a negative calcium balance. Presumably this is because rapidity of intestinal rate reduces the opportunity for absorption of all substances. Very high negative calcium balances are seen in the steatorrheic diarrheas where unabsorbed fatty acids tend to form soaps with the calcium; and, since vitamin D is fat soluble, vitamin D deficiency almost invariably coexists. So far as we are aware, there is no evidence that calcium is *excreted* by the large bowel. The occasional presence of more calcium in the feces than has been ingested may be explained by failure to resorb all that has been secreted with the digestive juices, which being a volume of more than 8 litres per day[20] would contain nearly one-half a gram of calcium.

The paths of exit for the calcium which has gained access to the body are thus confined to the digestive juices and the urine. Little is known about the mechanism of urinary calcium excretion. If, as has been assumed, the glomerular filtrate contains the diffusible fraction of the plasma calcium, then 9 grams of calcium would be filtered per day, of which 99.8 per cent must be resorbed by the renal tubules.* Albright

* Circulation based on 125 cc. glomerular filtrate per minute and 200 mg. calcium appearing in urine in 24 hours.

has stated[1] that the "threshold for calcium excretion in the urine is about 7.0 mg. per 100 cc.," implying, of course, that other factors, including serum protein concentration, are normal. Hypercalciuria accompanying hypercalcemia would thus be readily understood, but it would also imply that at normal serum levels the urinary calcium excretion would be relatively constant. There are, however, many other factors which may influence urinary calcium excretion. For example, acidosis is accompanied by hypercalciuria without demonstrable change in the total serum calcium,[5] presumably by increasing the ionized fraction. Likewise in conditions of skeletal atrophy such as complete bed rest,[21] after major fractures,[22] in poliomyelitis,[23] in hyperthyroidism,[24] in certain phases of Cushing's syndrome, probably in menopausal osteoporosis, and in many other pathological conditions, hypercalciuria is found at some stage. In most of these conditions it is assumed that skeletal rarefaction is proceeding more rapidly than is new bone formation (resorption may be rapid or new bone formation practically cease), but in only rare instances is this transit of broken-down lime salts reflected in a rise of the *total* serum calcium. Furthermore, in experimental hyperparathyroidism the urinary calcium excretion may increase 100 per cent without appreciable change in the serum calcium level.[25] Many patients with a history of urinary lithiasis have been found to excrete excessive quantities of calcium in the urine on standard regimens without other abnormal findings,[26] and these patients have been termed "idiopathic hypercalciuria." Albright has even noted a few patients with hypoparathyroidism and low serum calcium who excreted large amounts of calcium in the urine; in one case there was an associated acute pyelonephritis and the hypercalciuria disappeared when the urinary tract infection was eradicated with penicillin.[27] Royster has found in two instances that more calcium was present in the urine of a diseased kidney than from the good side.[28] Thus there are so many factors which seem to play a role in the elimination of calcium by the kidneys that interpretation of quantitative data is extraordinarily difficult. Diseases of the kidneys with bilateral alteration of renal function add further confusion, for though some patients with severe hyperparathyroidism and renal insufficiency have exhibited "normal" or low calciuria, the writer has seen the same situation with excessive urinary calcium excretion.[15] Until the *state* of calcium circulating in the body fluids in health and disease is clarified and the renal attitude toward the

various calcium fractions is understood, the role of the kidneys in calcium metabolism will probably remain obscure.

Phosphorus Transport and Homeostasis. The difficulties of interpreting phosphorus balance in relation to bone physiology have been mentioned. In contrast to calcium, most of the ingested phosphorus is normally absorbed and excreted in the urine. The concentration of phosphorus* in the serum (almost entirely inorganic phosphorus)[29] is a reflection of how much is entering and how much going out. Normally the diet provides the bulk of the phosphorus entering, and the urine is the way of escape for most. Changes in dietary phosphorus are usually quickly reflected in the serum phosphorus concentration. This may be demonstrated in renal insufficiency where the urinary phosphorus excretion is characteristically reduced and serum phosphorus is high. Administration of one of the phosphorus precipitating agents (such as aluminum, iron or excess calcium) to the diet rapidly results in a fall of serum phosphorus. In total starvation, however, the serum phosphorus rarely falls appreciably because, in the breakdown of protoplasm needed to provide energy, considerable quantities of phosphorus are released. But when carbohydrate is provided to minimize the protein catabolism in starvation, serum phosphorus rapidly falls. Little is known about the homeostatic mechanisms for phosphorus in the serum; youth and actively secreting pituitary eosinophilic tumors of acromegaly are associated with higher serum phosphorus concentration than is found in the normal adult.[30] However, there is no evidence known to us that the bone salts support serum phosphorus homeostasis in time of need, as they clearly may in the case of calcium homeostasis. The *concentration* of phosphorus in the extracellular fluid is clearly of importance to bony physiology (vide infra); and since the serum phosphorus is generally assumed to be wholly diffusible in normals, serum phosphorus level must have a decided influence on skeletal metabolism.

Calcification Mechanisms of Cartilage and Bone. We may now turn to a visualization of the metabolism of the skeletal structures themselves. Bone formation depends upon a specific cell known as the osteoblast. Under certain influences an organic matrix is elaborated about this cell, even as collagen appears around fibroblasts; and our current concept is that collagen and bone matrix are closely related substances. Indeed fibroblasts can be induced to produce bone,[31] for example, when

* The terms serum and extracellular phosphorus used in this paper denote the phosphorus of the serum which is inorganic phosphate.

urinary tract epithelium is implanted into the rectus sheath. The difference between collagen and bone matrix (osteoid) is that the latter normally calcifies almost immediately on being laid down; the former does not. There is thus some property in osteoid which renders it calcifiable in the same fluid medium in which other tissues do not calcify. In similar fashion cartilage normally reaches a stage of development in which its matrix calcifies. Calcium deposition is very different in cartilage and bone, and much more is known about the former. A brief perusal of the research on this subject seems profitable.

Most bone formation takes place on a scaffolding of cartilage, and growth of the skeleton results from multiplication of the cells of these epiphyseal cartilages. As the cartilage cells at an epiphysis mature, they increase in size, and the interstices—i.e., the matrix of the most mature cells—become calcified. Capillaries grow up from the bone side of the epiphyseal line into the rows of swollen cartilage cells, bringing with them osteoblasts. These osteoblasts lay down a matrix in which lime salts promptly are deposited around the calcified cartilage matrix. Almost immediately the bulk of the calcified cartilage matrix and its bony covering are resorbed; otherwise the bone would be extremely bulky and dense. All sorts of disturbances can occur in this process; the one which has received the most study is juvenile rickets. The classical studies on rickets[32] showed that the failure of calcification of cartilage was closely linked with the level of serum phosphorus, which is characteristically low. Not only could rickets be produced in growing animals by low phosphorus diets,[33] be corrected by administration of phosphorus, be prevented and cured faster by administration of vitamin D [34] in the presence of adequate dietary phosphorus, but also the cartilage of the rachitic animal was shown to calcify when placed in vitro with sera of normal infants or in artificial media containing adequate amounts of calcium and phosphorus.[35] So far as we are aware, no one has yet reported the in vitro calcification of the osteoid borders (uncalcified matrix around the bone trabeculae) which is also characteristic of rickets. There is little doubt, however, that an important cause of failure of normal calcification in this disease is a low serum phosphorus or what has been termed a low "solubility product" of calcium and phosphorus in the circulating fluids. Rickets also results from low serum calcium even with normal serum phosphorus.[36]

Early workers in this field visualized the lime salts of bone and

cartilage simply as precipitates of an ion product in supersaturated medium, but did not explain why the ion product of calcium and phosphorus should be supersaturated only at such places and not everywhere. The discovery of phosphatase in epiphyseal cartilage suggested to Robison and his colleagues[37] that this enzyme might locally elevate the concentration of phosphate ions by acting on some phosphoric ester substrate. However, they found that the in vitro calcification of cartilage in a medium containing sufficient $Ca++$ and $PO_4=$ was blocked by too low a concentration of inhibitors to prevent the action of alkaline phosphatase or to affect the concentration of bone salts. A "second mechanism" was therefore assumed.[38]

Gutman has studied extensively the role of the glucogenolytic cycle in epiphyseal cartilage. By histochemical methods it has been found that glycogen accumulates in considerable quantities in these cells prior to calcification. In summarizing his studies, Gutman has stated: "Calcification in cartilage is evidently a much more complex process than mere precipitation or the simple scheme proposed by Robison. It seems clear that enzymes other than phosphatase are involved. From the combined chemical and histochemical evidence, phosphorylative glycogenolysis would appear to be an essential part of the process *in its preparative phases*. . . . Whether glycogenolysis is essential in order to provide phosphorus in some special form or concentration or place, or whether required energy is made available is not clear."[39] Still another factor capable of locally elevating the concentration of phosphate ions was found by Levine when he demonstrated the presence of lecithinase in fetal cartilage.[40]

Physical and Chemical Structure of Bone. Some mention should be made of the contributions that physical chemistry has made to our present concepts of the chemical anatomy of bone. At a recent Conference on Metabolic Interrelations,[41] there was presented a comprehensive review of the subject. To summarize the present concepts: It appears that bone mineral, though not a pure chemical, or any single chemical individual, has a constancy of composition that is striking. It seems likely that tertiary calcium phosphate of some kind is the crystal structure and that additions to this crystal structure take place by adsorption or some other means. The basic lattice is probably of an apatite nature. Exchange reactions take place actively on its surface, much more slowly on the interior; some constituents become incarcerated into a

part of the skeleton from which mobilization is extremely difficult, whereas in other areas these same constituents are readily exchangeable and removable.[42]

That magnesium, strontium and certain heavy metals may substitute for calcium in the skeletal structures is well known. Since manufacture of the atom bomb much study has been devoted to the fate in the body of various elements which have to do with production of nuclear energy and which may be released in an atomic explosion. Extensive studies of the metabolic behavior of fission products have been made by Hamilton and his group at the University of California.[43] The major portion of many of the heavy metals is taken up by the skeletal tissues, and unfortunately they are removed extremely slowly by normal metabolic processes. The hazard of prolonged radioactivity from such elements is obvious, comparable to the disastrous late effects of the radium used in the plants making luminous dial watches.[44] A greater knowledge of bone metabolism is needed in order to combat deposition, and to foster the removal of such elements from the bones.

Observations on Cartilage and Bone Matrix and the Matrix of Pathological Calcification. Some years ago it seemed to us that current thought on bone physiology was giving too little attention to the stratum in which the lime salts were being deposited, and investigations were begun on the properties of the matrix. Albright in his classification of bone diseases had repeatedly emphasized that difficulties arising in the matrix might result in skeletal rarefaction.[45, 46] He postulated that the skeletal rarefaction seen in wasting diseases and Cushing's syndrome might be due to utilization of the protein of the bone matrix as a contribution to the general nutritional pool, and that no protein would be available under these circumstances for the laying down of new matrix.[47] It seemed likely that if matrix of a specific character is necessary before deposition of lime salt is possible, many things might go wrong in the processing of the matrix which might result in qualitative as well as quantitative imperfections. For example, the observation of Follis[48] that wide osteoid seams (uncalcified matrix) are a common postmortem finding in patients with chronic renal insufficiency seemed bizarre, since such patients have generally very high serum phosphorus and but little lowered calcium concentrations. Perhaps there might be some quality of the matrix which *necessitates* deposition of lime salts in the normal chemical environment, and the properties of the matrix

may determine the characteristic structural pattern of bone. Some of the studies resulting from these concepts have fortified our conclusion that if we knew more about the matrix, we would better understand calcium and phosphorus metabolism in bone.

For some time it has been known that skeletal and other tissues stain in a characteristic fashion to toluidine blue and to the periodic acid fuchsin technique.[49] Using these same techniques but, in addition, using fresh tissue slices, Levine, Rubin, Follis and Howard offered some new interpretations in regard to the processes of growth and calcification in cartilage and bone.[50] Metachromasia, a purple color as opposed to blue, depends upon an alteration in the light absorption of the toluidine blue when attached to highly polymerized compounds. The red color of the Schiff reagent (leucofuchsin) depends upon the formation of ketone radicles from adjacent hydroxyl groups. By suitable control observations the conclusion was reached that when the two reactions were both positive in bone and cartilage, it indicates the presence of an acid mucopolysaccharide.

Uncalcified cartilage is highly metachromatic and likewise stains positive with periodate fuchsin. Calcified cartilage is *not* metachromatic but stains pink with the periodate fuchsin technique. However, when calcified cartilage is very gently and briefly treated with acid, it becomes highly metachromatic to toluidine blue.[50] This is interpreted to mean that acidification has removed calcium molecules from acid radicles allowing places for toluidine blue to attach. Thus, contrary to previous thoughts on the subject,[51] the polysaccharide matrix does *not* disappear when calcification occurs. In the case of cartilage this polysaccharide is almost certainly chondroitin sulfuric acid, long known to be present in cartilage in high concentration.[52] In bone, which differs in many respects from cartilage, a similar situation was found. Osteoid (i.e., uncalcified bone) is both metachromatic and stains positively with periodic acid fuchsin. Calcified bone is not metachromatic; but when gently acidified, becomes metachromatic. Thus matrix of a polysaccharide nature is probably present in calcified bone, too.[52]

Rubin has noted that in the transitional zone of cartilage prior to calcification there is seen a characteristic sharpening and intensification of both these staining reactions. These changes likewise can be demonstrated in certain structures about to become bone. This has been demonstrated in tendinous and ligamentous areas where intensification

of the stains occurs in exactly the area which will change from fibrous membrane to calcified bone. Furthermore, the areas which have most recently calcified stain most intensely with periodic acid fuchsin. These observations were interpreted to mean that in the area about to calcify, there is an increased affinity for cations (toluidine blue), and more adjacent hydroxyl radicles have appeared, to be changed into keto groups by the periodic acid. Either more mucopolysaccharide has appeared or the chemical state of that already present has changed.[53].

Preliminary studies have shown that the hexosamine content of embryonic bone is greater than that of mature bone.[53] This finding augments the thesis that mucopolysaccharide is in greater concentration where bone growth is most active.

We were fortunate in having the opportunity at this time of studying biopsy material from a patient with generalized calcinosis. It was found that the calcified lesions contained an organic material which was metachromatic with toluidine blue and stained strongly with periodic-leucofuchsin reagents. The formed elements resembling crystals failed to stain with toluidine blue. The Von Kossa reaction (presumably identifying calcium) was positive in both the amorphous and crystal-like components of the smears. Heating a fresh smear over a flame produced first charring, then a white ash. The latter then failed to stain with toluidine blue or leucofuchsin, but the ashing produced no change in the microscopic appearance as compared with the fresh unstained smears. Decalcification with 1 per cent nitric acid produced no recognizable change of shape of the material but the consistency changed from gritty hardness to gelatinous softness; *the decalcified structure was metachromatic to toluidine blue* and the periodic acid fuchsin stain remained positive after decalcification. The conclusion was reached that the calcium salt was deposited in an organic matrix and that this matrix contained a mucopolysaccharide.[50]

Other types of human calcified tissues were then examined, and it was found that by these techniques arteriosclerotic plaques, calcified pericarditis, dental tartar and calcific renal calculi (with the exception of oxalate stones) all have contained a basic matrix with similar staining properties. These findings suggest that a mucopolysaccharide with specific properties is a basic component of almost all biological calcification.[54]

Parathyroid and Calcium Metabolism. In the discussion of general

factors influencing the concentration of the serum calcium and skeletal calcification, no mention was made of the parathyroid hormone or vitamin D. Since the preparation of a biologically active extract of the parathyroid glands by Collip in 1926, much knowledge has accrued on the physiologic properties of parathyroid hormone. As shown by Albright and Ellsworth,[55] injection of this hormone produces the following trend of events: increased phosphorus in the urine, fall in serum phosphorus concentration, hypercalciuria and rise in serum calcium. The classical clinical picture of chronic hyperfunction of the parathyroids demonstrates all these features; in addition there is a typical reaction of the bones, osteitis fibrosa cystica. But all patients with parathyroid overfunction do not manifest the skeletal changes either by x-ray[56] or pathologically.[57] There was a long polemic whether the primary effect of the hormone is on the body fluids and the bones are secondarily affected or vice versa.[58] The observation that even with the kidneys removed, parathyroid extract will cause osteitis fibrosa within a few hours in the rat,[59] proved that its action is not represented solely by inducing phosphorus diuresis and fall in serum phosphorus. The recent observations of Carnes seem to us highly important.[60] Rachitic rats, with wide osteoid seams, were given large doses of parathyroid extract. Resorption of osteoid (uncalcified matrix) occurred, as judged by the appearance of lacunae containing osteoclasts, just like trabecular resorption of *calcified* bone under the same stimulus. Similar observations were made by Rubin in the callus (uncalcified) of fractured fibulas in these rachitic animals after injections of parathyroid extract. It was also of interest that the rachitic rats showed but small rise in serum calcium and no metastatic calcification of the kidney, in contrast to rats on ample calcium and phosphorus diet where the same doses of parathyroid hormone produced higher serum calcium and extensive renal calcification. The explanation would appear to be that bone *matrix* may be destroyed as a result of the activity of parathyroid hormone, regardless of its mineral content, and that the magnitude of the rise of serum calcium and the production of metastatic calcification are in part at least governed by the mineral content of the reabsorbed matrix. This is another example of the well-known fact that matrix and lime salt go together in skeletal resorption,[61] and that the bone is attacked not primarily by resorption of the salts but by disintegration of the matrix.

Vitamin D and Calcium Metabolism. It has already been mentioned that vitamin D increases intestinal absorption of calcium.[18] But there must be other physiological effects of this group of steroids. In hypoparathyroidism, where the serum phosphorus is high and urinary excretion of phosphorus low, administration of vitamin D, in large quantities at least, results in sharp increase in urinary phosphorus. A distinction has been thought to exist between the effects of "therapeutic" and "toxic" doses of vitamin D.[62] Relatively small doses alleviate the manifestations of rickets (vitamin D deficiency), but large doses overcome all the distinguishable clinical and blood chemical alterations of hypoparathyroidism.[62] In arthritic humans, heavy doses of calciferol not infrequently result in hypercalcemia with disastrous effects on the kidneys.[63] Recently Anning, Dawson, Dolby and Ingram[64] have found that the first detectable evidence of D intoxication in their group of patients with skin tuberculosis was an elevation of the diffusible fraction of serum calcium (without change in the total serum calcium).

Animals can be easily poisoned by vitamin D with resulting widespread changes.[65] Amazingly enough, there are wide osteoid seams (indicating uncalcified bone matrix) despite the high total serum calcium and phosphorus.[66, 67] This discrepancy and the previously mentioned observation of uncalcified osteoid in renal insufficiency[50] suggest that in both these conditions the osteoid may *be abnormal and not calcifiable.* It is not known whether renal insufficiency, a common result of vitamin D intoxication, is a requisite for the production of excessive osteoid in D poisoning; it would probably require an artificial kidney to maintain serum electrolytes at normal concentrations during experimental D intoxication to clarify this point.

Early in the poisoning of young rabbits by vitamin D, the histologic appearance of the bones indicates a stimulus to great osteoblastic proliferation and new bone formation, soon followed by bone resorption.[67] In vitamin D deficiency urinary calcium excretion is usually very low, and it is interesting that calciuria rises much more slowly after administration of the vitamin than does the serum calcium, as exemplified in a study of resistant rickets by Kyle.[68] Thus there are multiple evidences that vitamin D has widespread and complex physiological activities on many bodily systems.

Some Thoughts on Calcium Transport in Body Fluids. The fundamental studies of McLean and Hastings on the state of calcium circulat-

ing in the blood plasma disclosed that normally the ionized and diffusible fractions are practically equal, that one half of the total calcium is in the ionized state, and that in the hypercalcemias studied by them the ionized fraction maintained a fixed relationship to the total plasma protein.[9] We are not familiar with any studies of pathological sera using the biological technique of the frog's heart since that time. However, clinical observations have disclosed that many disease states other than hyperparathyroidism may be associated with elevated total serum calcium concentration—rapid skeletal atrophy with or without the stimulus of widespread metastatic cancer, sarcoidosis, myeloma, Hodgkin's disease, breast and lung cancer without clinical or pathological evidence of skeletal disease.[54] In some patients with sarcoid and myeloma, hyperproteinemia coexists with the hypercalcemia, but equally often there may be hyperproteinemia without hypercalcemia and hypercalcemia without hyperproteinemia. Furthermore, we have never met with a case of hyperparathyroidism in which hyperproteinemia was present. All types of diseases associated with hypercalcemia that we have studied have exhibited hypercalciuria and a tendency to vicarious calcification, including hyperparathyroidism; but in the latter disease the spinal fluid calcium concentration tends to be normal or barely elevated, whereas in the others it closely follows the diffusible calcium concentration of the serum as calculated on the McLean and Hastings nomogram. No satisfactory explanation for this has yet been offered, but there must be something different about the circulating calcium in hyperparathyroidism that is recognizable to the tissues which elaborate and resorb the cerebrospinal fluid.[54]

During the studies on bone and cartilage matrix mentioned above, in which the conclusion was reached that such matrix contains an acid mucopolysaccharide, it occurred to us that such a constituent might at times circulate in the body fluids. The theoretical "binding" or "carrying" power of such a material would be many-fold that of proteins, and such changes in such a fraction might be reflected by wide fluctuations in the total serum calcium.[54] No concrete evidence on this hypothesis has so far been adduced. But Park has always insisted that from the histologist's point of view, bone is not dissolved leaving organic matrix behind; it is necessary to think of the organic matrix, in which the lime salts are imbedded, as being dissolved or disintegrated at the same time.[69] McLean and Bloom[70] have observed in parathyroid poison-

ing, movement of bone mineral from the zone of osteitis to the venules in the proximal marrow spaces. With Von Kossa stain of undecalcified sections, they identified this mineral both inside and outside phagocytes in the marrow and noted its association with a stainable matrix. Carnes, Levine and Rubin[71] have demonstrated that this matrix, in which bone mineral is localized, stains strongly with periodic acid fuchsin and gives other staining reactions characteristic of bone matrix. Though by no means positively identified, it may be that they have observed matrix polysaccharide moving to the blood with the lime salts in this type of bone destruction.

Only mention will be made of the effects of androgenic and estrogenic hormones on bone metabolism. As Park has aptly expressed it, "endocrine regulation of bone growth is too confused a topic at present even for speculation."[2] It would only confuse the issues now to review the spectacular effects of certain of these hormones on calcium metabolism in amphibia, birds and certain mammals, since so little of this information seems applicable to man. Gardner and Pfeiffer[72] have recently reviewed the information on the reaction of bone to sex hormones, and the reader is referred to their article.

In summary it may be said that in the present discussion there has been presented in a most unorthodox manner some of the experimental and clinical evidence upon which rest our present concepts of bone physiology. Many hypotheses and enigmas have been included. However, one cannot help believing that all these things will one day fit into a clear, simple and definite pattern when the light of knowledge falls fully upon them. I do not expect ever to understand why a given cell in an embryo alters at an early date so that even if transplanted to another site or grown in tissue culture, it will maintain its identity and develop eventually into a femur. But it seems not impossible that before too long we may have some insight as to why fibroblasts of the rectus sheath can be induced to become osteoblasts by proximity with urinary tract epithelial cells; why the presence of one type of cancer cell in a bone causes osteoblastic proliferation and another causes osteolysis; why certain necrotizing tissues deposit calcium salts and others do not; how a physical force such as strain can be transplanted into a stimulus to bone cell proliferation and physiologic activity; how an increase in venous pressure can cause faster and greater bone growth.

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TUBERCULOSIS OF BONES AND JOINTS*

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It is a strange paradox that the more one becomes acquainted with any subject, the less competent one feels to be didactic in regard to it. So your author of this evening in regard to tuberculous involvement of bones and joints. A mass of material and a mass of literature in the many past years have pointed the way and molded opinions, and yet in this relatively well established subject change is continuously taking place, and surprisingly so in the past few years.

All such lesions as these, one must understand, are never contracted by direct infection. Seeding of such lesions must occur either through bloodstream infection, lymphatic channels or continuity of tissue from other preceding tuberculous foci frequently minimal in amount and often at considerable distance. If one can finally come to the realization of two facts, a chance of proper diagnosis of such lesions in an earlier stage may be accomplished.

First, such tuberculous lesions almost invariably are slow of development, prolonged in their primary period of pathological destruction, and yet fulminating in their last or disastrous stages. Hence the true nature of such lesions at first is frequently overlooked and the condition usually misdiagnosed. Syphilis has been called the great masquerader but, with the spotlight upon it, now takes second place to the role of tuberculosis as such. Any low-grade, slowly progressive inflammatory condition of bone or joint may be tuberculosis. Rarely is the condition acute. Hence most lesions of this nature are treated over a period of months or even years before final disaster of sinus breakdown or rapidly increasing disability suggests culture or pathological study or forces biopsy. This situation is enhanced by the fact that most such chronic, slowly progressing lesions actually are what they seem, non-

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tuberculous and rarely benign. Hence justification for biopsy early, to definitely determine the basic condition, rarely seems essential. Yet it would seem to us at Sea View, where we see the end results of delay, that even if many biopsies were done with only a few resulting in positive findings of tuberculosis, the avoidance of late destructive cases coming to our attention justified all of the investigative work and biopsy procedures. Therefore, let one's suspicions be aroused by the chronic inflammatory condition which gradually progresses.

Secondly, once established, advanced tuberculous lesions of bone or joint are in their end results almost as disastrous as carcinoma and almost as difficult of control. Early surgery, combined with the protection rendered by antibiotics (streptomycin) promotes a high percentage of arrests or so-called cure, and in this respect of course far exceeds expectations in carcinoma. The comparison, however, as far as disaster and life expectancy is concerned, where far advanced infection of tuberculosis exists is a fair one to those of us who have these cases presented to us.

To review briefly past literatures on this subject, especially that of didactic nature or acquired from textbooks, invites one to modify previous views to a considerable extent.

Etiology: All such lesions, of course, are based upon the presence and viability of the tuberculous organism of bovine, avian or human type. In the overall picture of the progress of such lesions, or orthopedic care of them, the type of the invading organism is of little interest as far as treatment is concerned or outcome is determined. Much has been said as to the influence of age in relation to outcome. True, growth factors in children and destruction of epiphyseal lines or growing structures will modify the end result as to function of the parts involved but they have no influence on result as regards the mode of treatment to be used or the recovery results to be obtained. Heredity and race have been noted as an influence with certain races susceptible and others resistant. End result studies on several occasions at Sea View have shown that the so-called susceptible races, given equal opportunity as to surgical and medical care, rest, food and antibiotics have progressed as favorably as the so-called resistant races.

The influence of trauma on localization, aggravation, or spread of tuberculous bone or joint lesions has been and probably will remain for some time a very argumentative matter. We would believe that

single localizing trauma to an already infected lesion of this nature could and does stir up latent infection or further alight active process. We would also believe that single solitary trauma (fracture or severe solitary injury) could and does on occasion form damaged tissue within the body satisfactory for culture and localization of tubercular organisms where hematogenous bacteremia exists. The fact that development of solitary tubercular foci following single localizing trauma in patients with active tuberculosis is rare cannot, to our minds, vitiate the fact that it does, on occasion, occur. Consider the patient with positive chest, Gaffky positive sputum, fracture of the femur, aspiration of the hematoma and culture of tubercular organisms from the hematoma. We have seen this same situation repeated. Bloodstream infection resulting in a single osseous focus of tuberculosis must at the same crisis of the seeding process have inoculated innumerable other areas even though none developed clinically. Something must have created favorable conditions where localization took place. The history and progress of the lesion often point to trauma. Conversely, to establish trauma as the initiating factor in the development of such a lesion, symptoms should occur within a reasonable period following such injury and the progress in destruction must parallel that to be expected in a similar lesion of like duration.

The incidence of bone and joint tuberculosis has tremendously decreased in the past thirty years due to preventive measures. Control of food supplies such as milk, butter, etc., with pasteurization, segregation of the tuberculous patient, education of the general population, and conversion of open to closed lesions more rapidly by better medical and surgical care, have worked a minor miracle in reduction of number of patients infected. Still, with a city of many million people, a basic considerable residual of such lesions continues to exist and to develop. Hence at Sea View Hospital in our city still exists one of the largest services in the world handling tuberculous bone and joint lesions.

Diagnosis: Much in the past has been made for diagnosis of such lesions by swelling, effusion, atrophy, deformity, spasm, protection, destruction, shortening, sinuses, night cries, pain, etc. If one could place an attitude of suspicion of any chronic structural lesion as the foremost factor in diagnosis, cases would be apprehended much earlier and results would be much less destructive. All of the old criteria for diagnosis represent late lesions with considerable destruction. Indeed, the

earliest possible diagnosis represents considerable involvement and symptomatology as outlined above represents almost an end stage.

True diagnosis as stated should represent a chronic lesion of bone or joint not rapidly amenable to routine measures. It is slowly progressive and rarely painful until fragmentation has occurred. The progress is almost always slowly destructive and rarely productive. Suspicion should be confirmed by early biopsy, culture, tissue section and guinea pig inoculation. Sedimentation rate and skin tests are frequently fallacious. Note the patient with tuberculosis involving half the length of the spine with negative tuberculin skin tests even 4½ months following operative procedure, with proven culture and positive guinea pig. Note cases with single and multiple involvement, simple and overwhelmed alike, with sedimentation rates of two to ten. Note the concept that a positive skin test may mean nothing since the mass of the population has in the past been infected, resistant and recovered; that negative skin test rules out tuberculosis when in fact it does not. The findings of temperature rise, weight loss, retarded growth, local reaction, etc., are as true in syphilis, tumor and other infections, etc., as in tuberculosis.

Remember the old proverb that "the waters from the eaves drip in the same old holes." In chronic disease of bone or joint be early to suspect, biopsy, prove!

From a roentgen viewpoint, soft tissue changes and shadows are much more important as to early diagnosis than the changes in the bony structures. Non-osseous changes may be represented by general swelling, erasure of normal soft tissue markings or unusual enlargement of certain muscle sheaths or fascial spaces. Bony changes may show atrophy, destruction, lysis of cartilage with decrease of joint space or, in children, expansion with spina ventosa. Rarely productive changes occur.

Prognosis: The best guide for prognosis as to final outcome on these patients is still that presented by Mather Cleveland in 1939. Prognosis depends more on the amount of general involvement than upon the amount of or stage of destruction of the solitary lesion which may be under consideration. Cleveland classified patients into four groups and gave percentages of mortality as follows:

(a) Those with no evidence of pulmonary tuberculosis (11.2 per cent).

(b) Those with pulmonary tuberculosis, negative sputum and no metastatic spread to other organs (7.5 per cent).

(c) Patients with pulmonary tuberculosis and positive sputum (40.4 per cent).

(d) Patients with pulmonary tuberculosis and negative sputum with metastatic spread to other organs (61.5 per cent).

This not only is a good scale on which to match your patient as to possibility of outcome, but also is a warning for thorough investigation of all such patients before final consideration as to surgery. He remarked on the improvement in results being secured, particularly in group (c) where positive sputum existed with pulmonary tuberculosis, by improvements in thoracic surgery. This steady improvement in statistics in cases with pulmonary tuberculosis, and even in patients with metastatic spread, by associated improvement in surgery and medical care, has steadily continued. Add to this the advent of streptomycin and the improvement in statistics among bone and joint cases has increased even further. However, the basic conditions stipulated by Cleveland for prognosis still hold approximately in the same proportionate percentage among the four groups. Despite the bad prognosis when a patient is received with multiple joint infections, with possible positive sputum and even with metastatic spread to other viscera, frequent brilliant results are obtainable and rehabilitation of such patients has been accomplished by prolonged, undiscouraged, coöperative medical and surgical care. One should never be discouraged at the outset nor through the course of care of such a patient. Reconstructive work in attempt to save the patient may take tremendous effort and prolonged time. Discouragement can only lead to defeatism and withholding of necessary care, medication, antibiotics and surgery on the basis that it will be wasted in a particular instance and could be better applied elsewhere. On many occasions at Sea View patients apparently doomed on arrival have eventually left the institution ambulatory and returned to self-support. The least hesitancy as to determination to save them would have proven disastrous. Only when the patient has finally succumbed should one's efforts cease. The balance may shift even late in the disease. The struggle to save patients with such lesions is so great and so long that disbelief in possibility of favorable outcome is bound to exist unless the personnel handling them have had many years of close association and observation with such work.

Such patients were reconstructed before the advent of streptomycin. With the advent of streptomycin the recovery of severely involved patients became more frequent and more rapid of achievement. While streptomycin has given us great benefit it has also carried with it increasing problems. Many more patients survive and the problems of reconstruction on the survivors have become greater.

The Importance of Exhibits vs. Lectures

With the above somewhat generalized outline of the problems set forth, considerable furtherance of knowledge can be provided by a selection of material and its grouping in exhibit form. Where the stability of numerous correlated photographs, prints, charts, photomicrographs, etc., exist, which can be referred to and again reviewed, time is permitted for a gradual molding of ideas and opinion beyond that given during the rapidly moving course of a lecture or talk where one may not turn back page by page or print by print for comparison.

Roughly the pathology of tuberculosis consists of the invasion of tissue with an organism producing a toxin causing round cell infiltration which eventually becomes so great that the tissues break down in caseative necrosis progressing to a state of fluid necrosis, fragmentation and destruction. Where bone or joint structures exist, problems are increased beyond the ordinary by the slowing down of the disease and the reconstructive processes and the possible development of large masses of inert hard foreign material.

Tuberculous lesions heal mainly by protective fibrosis and calcification tending to seal up the gangster tubercle bacillus in a concrete coffin and maintain him there, though unfortunately still alive, still viable. This has a direct bearing upon such lesions where joints are involved. There the protective mechanism of fibrosis and calcification becomes placed in a mill wherein the enclosed lesions are ground up and the living bacilli again freed.

Similarly, where bony structure is involved in the tuberculous process, collapse and fragmentation grind up the protective encasement of the bacilli and set them loose for reactivation of disease process.

The Method of Production of Gross Changes

In bone and joint structures pathology is grossly produced in a manner frequently at variance with that in soft tissue lesions. It is often

more destructive and more permanent as to outcome. The mode of production of damage can be, for convenience, grouped under several headings. Usually several of these factors are present in any given case. They are:

INFLAMMATION.	ABSCESS BULK.
DISEASE EXTENSION.	SECONDARY INVADERS.
ENDARTERITIS.	DEFORMITY.
STRIPPING.	PATHOLOGICAL FRACTURE.

Inflammation. Inflammatory changes may occur around a bony or joint structure or throughout its tissues. Such inflammation developing from the tubercular organism is peculiar in two respects. It causes caseative necrosis instead of coagulative necrosis and there is atrophic response exhibited by osseous structure to the tubercular toxin regardless of the disease process itself. The atrophic or lytic effect of tuberculin toxin may extend for a considerable distance beyond the actual inflammatory location of the tubercular disease. Bony changes may occur predicated upon the tuberculin toxin even without the presence of the tubercular organism where such atrophy exists. Weakness and deformity may result to a considerable extent dependent upon such atrophy both as to internal osseous structure and as to size or growth of bone. Occasionally despite the destructive inflammatory or bacteriologic factor the gross changes in bone or joint structures may progress in a nature similar to non-tuberculous osteomyelitis or arthritis. This is rare. Bone expansion, sequestration, involucrum and the findings of suppurative arthritis of a joint, non-specific, are occasionally seen. Since the process develops slowly tissue reaction is delayed. Hence, as in any low-grade osteomyelitis, the roentgenogram findings may show a picture resembling certain forms of neoplasm. Conversely the slow-growing neoplasm, mildly destructive, with associated soft tissue bulk, has been and will in the future be occasionally confused with tuberculosis until biopsy or final outcome discloses the true nature of the lesion.

Disease extension. Extension of the disease by continuity of tissue throughout the structure involved or to nearby organs or structures can greatly increase local damage or prejudice the individual's chance of survival. The inherent low-grade process causing little bodily reaction, being mainly destructive and rarely productive, permits of such

extension far beyond that permitted by body reaction to other more active infections or rapidly developing lesions. The lack of any severe symptomatology tends to delay realization of the true nature of the disease process under observation and treatment to arrest it. Tissue irritation is at a minimum from the products of the disease until bony collapse occurs with spicule fragmentation which mechanically stabs the patient into recognition of pain, or until gross alteration of joint surfaces disables him.

Tuberculosis of the spine with unrecognizable involvement thereof may extend around a rib causing practically asymptomatic chest wall abscess. Pleural ulceration and final break through the lung into a major bronchus may occur before any except the most innocuous symptoms exist.

Consider a patient with a mass of fluid abscess material retroperitoneal and along the psoas sheaths communicating with the thigh to such extent that a quart or two of fluid may be pressed back and forth from the retroperitoneal space into the thigh by ballottement with the patient completely asymptomatic. The minor nature of nerve irritation caused by this process has been seen in innumerable other instances of disease extension. It helps to account for the fact that tuberculosis of bones and joints can develop to disastrous extent, with little if any complaint, and untreated.

Endarteritis. Obliterative endarteritis is one of the outstanding findings in microscopic pathology of the tubercular process. It is a gradually progressive process. Where such process exists near bone and gradual shutting off of blood supply and nutrition thereto is accomplished, specific pathological reaction occurs independent of the reaction to the tubercular organism. This is another strong reason for confusion in clinical diagnosis of such involvement. The tubercular toxin causes atrophy of bone, and the gradual robbing of the bone of its blood supply causes calcification and sclerosis. An intermingling of the two processes may come to such a balance that no actual bone change is demonstrable until collapse occurs. Excessive endarteritis may throw the balance in favor of productive changes causing apparent sclerosis in x-rays of such a patient; even of productive changes resembling hypertrophic arthritis. When this occurs in a chronic lesion, what chance has the diagnostician of making a proper decision until, late in the disease, abscess formation or sinus development accords true recog-

nition of etiology?

Stripping. As steady disease extension occurs along a bony structure in continuity, either of a long bone or of the spine, the formation of abscess products and caseation mechanically may lift periosteum or ligamentous structures from the bone. Immediately nerve supply which goes directly into the bone through Volkmann's canals from periosteal covering is cut off. Nutrition to the cortex is likewise immediately removed and soon nutrient vessels are blocked or torn and blood supply denied. When this process occurs slowly, productive changes may have taken place only to be interrupted at various stages. Where the process takes place more rapidly, no bony productive changes will be permitted and the stripped bone becomes dead and inert to tubercular bacterial action or tubercular toxin alike. Such completely stripped dead areas of bone retain the same specific gravity they had while viable and alive. The result is that roentgenogram thereafter, which interprets structure only through its specific gravity, shows no change from the normal. Hence large areas of bone which are so stripped may be, and often are, falsely interpreted as uninvolved and intact. After such involvement diagnosis of lesion, prognosis as to outcome, and judgment as to surgery, stabilization or treatment must depend upon soft tissue shadows (abscess). This fact gives one an insight into determination as to extent of fusion of a spine. Such fusions to be adequate cannot be based upon the old decision to fuse two vertebral bodies above and two below the involved vertebrae. They must be extensive enough to cover totally any abscess shadows shown or, in a known case of tuberculosis of the spine, to cover the extent of any abscess shadow shown and any mottled vertebral bodies seen. Where any such entirely stripped and dead bony structure exists, and is impossible of removal, it may act as a permanent sequestrum. Since microscopically minimal production is seen to occur in tuberculosis, the reorganization of such sequestrum may eventually be accomplished after months or years if mixed infection has not occurred through sinus formation. Where mixed infection has occurred, sequestration may be permanent, but more of this later.

Abscess bulk. Abscess bulk in itself, and disregarding any factors of pressure, represents grave pathology to the body as a whole. The thickened peripheral limiting fibrosis is relatively impermeable. Despite this the necrotic contents in the viable patient must be and are gradually

absorbed and the remaining detritus calcified. The steady thickening of the fibrotic wall and contracture thereof is evidence of body irritation continuously present and progressive. Though body reaction and toxemia may not be appreciable, it must be and is present. Now that streptomycin and other antibiotics are at hand for restraint of mixed infection, the question of evacuation of such abscesses more constantly arises. Usually repeated aspiration can be carried out until surgical stabilization and fixation of the causative focus stops further formation. By repeated aspiration (500 cc. three times a week for three months or more has been done) the general bodily structure may be relieved of the deleterious effects of natural resorption of this material. Even dorsal and cervical abscess pockets are susceptible to such repeated aspiration. Decision for incision rather than repeated aspiration usually rests on severe bodily reaction to an abscess pocket and this again usually is associated with mixed infection already present and without drainage. To incise such abscess, even with the use of streptomycin, unless essential, connotes carrying the patient into the valley of the shadow, and though recovery may occur with beautiful disappearance of the abscess, it merely means that that particular patient walked through the valley and happened to come out the right side.

Abscess bulk of itself by pressure upon other organs or parts of the body may promote severe pathological symptoms or disability. Lumbar abscesses have been seen so large that severe deformities were apparent through the clothing. A thigh has collected so much gravitating abscess material that the patient had difficulty in walking. Retroperitoneal abscesses are frequent offenders in the abdomen in causing symptomatology of gastrointestinal pathology actually nonexistent. Chest abscesses have embarrassed respiration. Abscesses about the spine have promoted back pressure to such an extent that paraplegia associated with tuberculosis and due to extradural abscess pressure alone, with no fragmentation of vertebral bodies, is commonly known. The abscess in and of itself, separated from any other part of the tuberculous process is frequently productive of great damage.

Secondary invaders. This lytic, chronic, slowly progressive, relatively asymptomatic disease gradually encroaching on other nearby tissue by continuity and causing minimal body reaction and fibrotic protection, should be expected to and frequently does finally involve the surface integument and break through the skin. Immediately sec-

ondary infection occurs with other organisms. The liquefactive material provided by the tubercular process represents an excellent cultural medium which such secondary invaders utilize. The process then becomes a combined one of caseative necrosis and coagulative necrosis. Stimulation of bodily response by the mixed infection almost always takes the form of increased productive changes. Such changes may be represented by more typical sequestration, involucrum, or even ankylosis of joint structures. Such ankylosis of joint structures through diseased areas has never been seen by us to occur in pure tuberculosis. It is frequent where mixed infection exists. Ankylosis may occur in tuberculosis as in the spine where vertebral collapse has caused continuous strain and stress on posterior ligaments and posterior elements outside of the diseased area, but such ankylosis through such stress strain must not be predicated upon the tuberculous process. Even where this exists ankylosis takes place only where the stress and strain are, leaving the ends of the disease process still open and free from fixation for furtherance of the tubercular disease. With the secondary infection and stimulation of bodily response also goes increase of bodily damage. Such increased damage may be denoted by development of amyloidosis as a late result or acute inflammatory reactions, temperature rise and prostration as the beginning. As we have said under abscess formation, delay or prevention of exposure of tuberculous processes to the surface and to mixed infection should be attempted wherever possible, and unless great gain is to be expected by the gamble. It is a strange thing that streptomycin is of minimal efficacy for ordinary non-tuberculous infections and yet of tremendous influence where mixed infection has occurred with tuberculosis and sinus formation. Much seems to be known about streptomycin, and yet to us it would appear that basically as regards its mode of action almost nothing so far is apparent. In our use of this antibiotic at Sea View the most outstanding benefit is the rapid achievement of improvement in general condition of the patient regardless of local status of the tuberculosis or mixed infection. Some strong metabolic influence seems to be at play. In such cases the effect on the secondary invaders appears to be dramatic and out of all proportion to what its effect would be in infections with similar organisms not based upon a primary tuberculous focus. While the drug's action in many instances on the tuberculous process and the mixed infection appear dramatic, in other instances the

gain is so slow that one is tempted to desist from its use. Prolonged periods of use are frequently essential, disregarding all such factors as resistance of organism or complications arising. If one considers it a retarding factor in the propagation of the tubercular bacillus and regards the tremendous bulk of involved tissue which the body must sterilize during the period of protection by this antibiotic, one can come to realize the long periods of time that may be necessary for its use before either it or natural processes can achieve a victory. Two years ago when a follow-up study of cases at Sea View with bone and joint tuberculosis and mixed infection was done, great criticism was provoked by the continuance of streptomycin beyond a ninety-day period for fear of developing a resistant organism. At that time cases were produced showing that on the percentage basis of development of resistance, continuation of the use of streptomycin had allowed us to achieve healing in many cases that must have been resistant. If by streptomycin one can slow down propagation of the tubercle bacillus, sterilize the sinus to other organisms and prevent readmission of other organisms to the still open sinus, one may achieve healing through any one of the beneficial factors of its prolonged use. How long should one continue the administration of streptomycin? Six hundred, seven hundred, eight hundred, nine hundred grams have been used in cases on our service with ultimate healing. Does streptomycin in itself and alone provide a favorable outcome? No, it only acts as a favorable factor slowing down the tubercular process, ridding the body of mixed infection, providing some unknown metabolic improvement, and giving us time for the influence of surgical procedures and medical care to be provided as in the past.

Deformity. Pathological changes in the tuberculous process are produced by development of deformity in itself and by its influence on other structures. Collapse of the dorsal spine will shorten and telescope the thorax on the abdomen. Hunchbacks do not live long. By compression and laceration of the spinal cord a deformity may paralyze. By flexion contractures of the hip or knee a patient is crippled. The influence of deformity continues long after the arrest of disease in successful cases. Knowledge of its possible development and prevention thereof is almost as important as the saving of life itself. Long acquaintance with end results alone can forewarn the attending physician and stimulate his interest in and determination to such prevention.

We have already called attention to the microscopic and gross pathological conditions demanding surgical fixation of weightbearing joints. Prevention of deformity reinforces this demand. What profits a human individual to live a reduced life span as a severe hunchback! Why allow a patient to continue with gradually increasing destruction for years until crippling deformity or shortening exist!

Pathological fracture. Collapse, compression and angulation of a tubercular spine is not usually regarded as a pathological fracture. Such it is. As one begins to broaden one's viewpoint, fragmentation at the hip, disorganization of the shoulder, etc., all become regarded as such. Not only are these pathological fractures but typical pathological fractures of the long bones incident to a basic tuberculous involvement occur. Where such situation arises, amputation is a frequent sequela. Pathological fracture, while not as frequent as some of the other factors in tuberculous pathology, must be considered a major one because of its implications.

The Factors of Failure

It is evidently impossible in any one dissertation, or indeed in any one individual's experience, adequately to cover the broad field of bone and joint tuberculous involvement. We will not, therefore, further enter into the discussion of the mode of treatment, the surgical procedures used, results obtained or regime of handling these patients. Rather we shall conclude this talk with a consideration of failure of recovery among patients where recovery should have occurred, all factors being considered. Why are there such failures? What is the basis in the individual case? How can we convert such instances to success or avoid their occurrence in the future? Some of the factors of failure, where one should have legitimately expected success, are not hard to find. Frequently their acknowledgment requires some self-criticism.

The failure to employ surgery. Where past experience has shown that surgery is indicated and yet has not been used really does not come under a factor of failure. By definition factor of failure states that one should have legitimately expected a success and yet failure occurred. To our minds one has no right to withhold surgery in these cases where past experience has so abundantly shown its value. It is beyond the limits of this paper to describe and defend the benefits to be secured by surgical fixation of weightbearing joints and occasionally surgical

resection of non-weightbearing joints. We shall assume in factors of failure that decision to surgery as applied to the individual case has been rightly used.

Inadequate surgery. Inadequate surgery does not imply that the decision to arthrodese was not properly taken. It implies all of the destructive pathological findings already given above which produce so frequently a complicated confused picture. Extent of arthrodesis in the spine may not always be possible of satisfactory decision. Destruction may extend unrecognized far beyond abscess shadows or mottled vertebral areas. Surgical fixation of a diseased area of the spine may cover all demonstrable disease and satisfactorily occur, only for one to find that lesions seeded beyond the area of the fusion developed further destruction. Because of increasing knowledge inadequate surgery is becoming more rarely a factor.

One should not be surprised when one's surgery is inadequate in extent or in amount. Note that we have mentioned the word "amount." We have seen solid light fusions of the spine placed through tuberculous posterior element disease gradually being cut across by surrounding soft tissue disease. We have successfully repaired these areas using more massive amounts of bone.

Inadequacy of surgery may exist in arthrodesis as to the type of bone used. It is not infrequent that sclerotic bone such as from the tibia will be seen to resorb gradually setting free the disease process by pseudarthrosis. There is little culpability of the surgeon to be found from inadequacy of attempted surgical fixation. Great culpability arises, however, from refusal to recognize such inadequacy and repair or extend such fixation when necessary. Arthrodesis if attempted must be achieved and if extension is necessary it must be extended. We have operated nine times on an eight-vertebra section of tubercular spine before securing continuity of fusion. The problems that face one in this type of surgery, and the knowledge that continued efforts may win, are not common property. The extent of arthrodesis of the spine need only be limited by the length of the spine. Patients have had spinal fusion from the occiput to the sacrum with arrest of tubercular involvement. Surgery must be adequate despite all difficulties if failure is not to occur.

Ineffectual surgery. Pseudarthrosis or failure of ankylosis of joints following surgery in tuberculosis is common. It is common in our

practice and will be common in that of others. Where destruction and deformity continue pseudarthrosis exists. It is frequently difficult to see on roentgenogram and is even more difficult of admission by the surgeon. Usually such pseudarthrosis whether of spine, hip or knee can be demonstrated by superimposed roentgenograms taken in the extremes of motion (bending views). Where disease progress exists, surgical exploration must be done even in the face of negative roentgenograms. Even on surgical exploration pseudarthroses are frequently difficult of visualization. They may be represented by a serrated crack, invisible until stressed motion of the part is made following surgical exposure. Even with wide open exposure and with forced motion of the part pseudarthrosis accounting for continued progression of disease may be extremely difficult to demonstrate and sometimes impossible to find. Repair of the suspected area with further addition of bone should be done in any such instance, whether the pseudarthrosis is demonstrated or not. For several years the danger of the presence of unrecognized pseudarthrosis appeared so great that we felt it imperative to explore every spine fusion before discharge from Sea View. Since Sea View cases disappear and are frequently impossible of follow-up study, patients returned to us with relapse of their disease incident to a pseudarthrosis which had been unrecognized by roentgenogram on discharge. As time progressed, by the use of better roentgenograms, superimposed flexion roentgenograms, noting lack of progress of deformity over many months' observation, and observing subsidence of active disease, the patients with solid arthrodesis could be ascertained. Progress of disease, progress of deformity, local tenderness in a supposedly solid fusion area, continuance of abscess formation or sinus drainage in a patient under adequate care almost always indicates pseudarthrosis whether demonstrable by roentgenogram or not. Even with the improvement afforded by streptomycin, continuance of sinus drainage in a patient supposedly with adequate ankylosis almost always denotes ineffectual surgery.

Bony pocket (*developmental*). Failure of arrest of the lesion and recovery of the patient under otherwise adequate care may be based upon the presence of a developed uncollapsed bony pocket. There, sclerosis, lack of blood supply and impossibility of drainage may cause continuance of symptomatology and disease even where adequate fixation is present and even where use of large amounts of streptomycin

has been provided. Since the specific gravity of the contents of these pockets may remain relatively unchanged from that of the preceding normal bony structure, ordinary roentgenograms may not demonstrate such a condition and permit of surgical eradication. Sterilization of such a pocket may require such length of time that the use of antibiotics becomes of theoretical value only (many years). Where such a lesion exists where its removal is impossible because of danger to the individual (centrum of vertebral body), one may have to concede failure as to complete recovery and accept the poor compromise of an asymptomatic active patient carrying around a known focus of infection within the body. As surgical experience advances more some such lesions can, however, be removed successfully.

Bony pocket (*surgical*). A similar situation may arise following surgery, either by failure to uncap a developmental pocket while doing arthrodesis or by separation of bony parts due to arthrodesis. The implications remain the same as where developmental bony pocket exists. Unfortunately one cannot foresee the occurrence of this situation. As in the developed pocket, surgical eradication will be necessary or acceptance of a compromise situation result. Fortunately in the case of both the developmental and the surgical pockets their eradication may be possible if one suspects their existence. Planagraphic roentgenograms should be made on suspicion of such a lesion.

Sequestrum. Tuberculous involvement of bones is an osteomyelitis. Sequestra may form as a result of disease invasion or, as has been shown above under pathological fractures, as a result of stripping and denudation. Again healing cannot be expected to occur within any reasonable length of time unless the sequestra are removed. Fortunately fragmented vertebral bodies representing minute sequestra are usually removed by the normal reactive processes of the body tissues. Where large fragments or whole vertebral bodies, however, have been entirely stripped, they may lie dead and inert for years without change, continuing as a hard foreign body within the tissues and promoting a favorable locale for continued activity of tuberculous infection. In such instances again compromise must be had. Usually in the spine with complete fixation the process remains inert. Elsewhere sequestra usually continue asymptomatic disease activity. As in osteomyelitis from other pathogenic organisms this may demand repeated attempts at sequestrectomy before recovery can be expected. Formation of a seques-

trum of any size certainly has been a factor of failure in our hands. If the condition is suspected and looked for, surgery can usually be provided with favorable result. Again planagraphic roentgenograms may be necessary. As in the presence of bony pockets, pseudarthrosis, inadequate surgery, and all of the other factors of failure, suspicion is usually late and recovery delayed thereby.

Visceral involvement. This factor one would suppose could not be laid at the door of the orthopedic surgeon. Actually frequently it may be justly attributed to his care. Early diagnosis and early effectual adequate surgery may arrest the disease before such spread occurs. It is not well known or realized, for instance, that tuberculosis of the rib is actually tuberculosis of the spine with extension of abscess around the rib first becoming appreciable as a mass on the chest; that spinal fusion widely covering the area of vertebral involvement (though this may never be seen by roentgenogram) will control the so-called tuberculosis of the rib and result in healing. Where such steps are not taken continuation of activation of the apparent rib lesion may occur resulting in perforation through both layers of the pleura into the bronchial tree, sudden tuberculous pneumonia and death.

Considering the above one should not expect the abdominal viscera to long lie in contact with retroperitoneal abscess masses without similar situations arising. This, then, leads directly back to the orthopedic surgeon as to decision for surgical fixation 1) because of the basic pathologic lytic nature of the lesion, 2) to prevent deformities, and 3) to shorten the disease and prevent complications.

Such factors causing failure through development of visceral involvement occur despite the best and most rapid surgical fixation and medical care. Consider the patient with tuberculosis of the spine, progressively fused in stages from cervical 5 to the sacrum with the securing of solid ankylosis and complete arrest of further progress of the spinal disease. Thereafter a slowly progressive complaint of upper abdominal pain and a final disaster occurring with rupture of dissecting aneurysm of the aorta. Note then the pathology found at autopsy with intimate involvement of the aortic wall with low dorsal tubercular abscess mass. Yes, visceral involvement may be a factor of failure defeating the best of care as well as a matter of neglect.

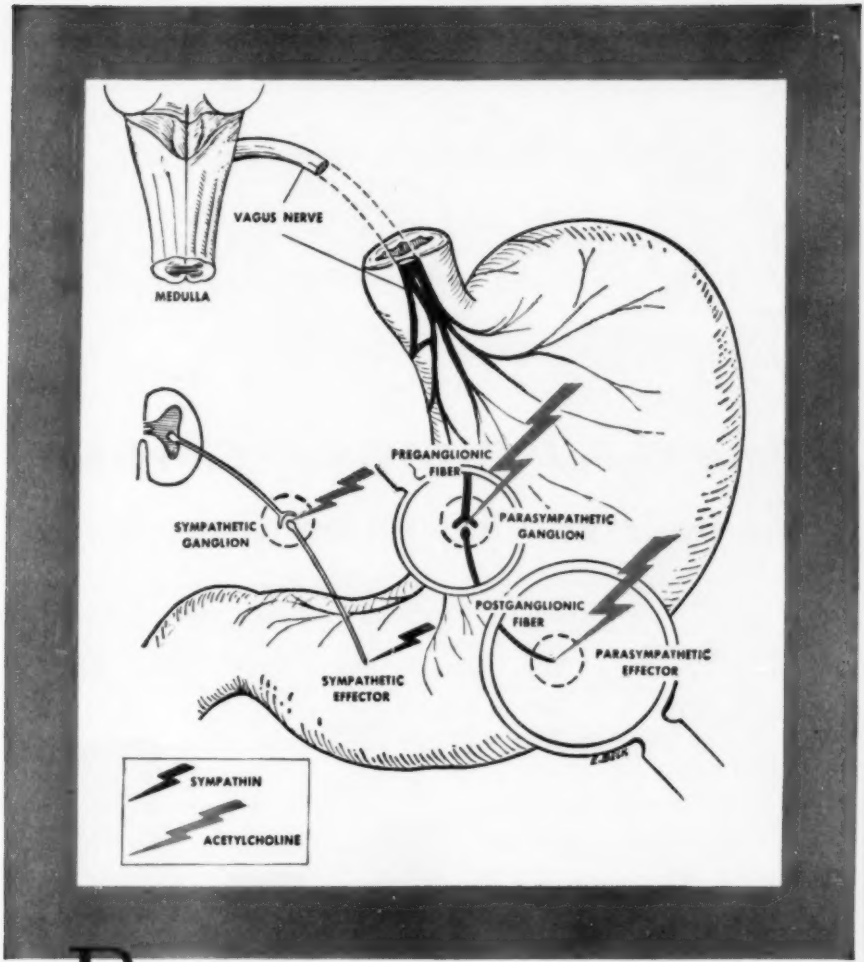
Complications. General medical and surgical complications of all sorts, of course, are factors of failure beyond our control. These we

will not discuss. The complications which are factors of failure we would call your attention to are the complications resulting from treatment and forcing the interruption thereof. Streptomycin not only is beneficent but also may prove toxic. Occasionally allergic manifestations may force reduction or termination of its use. When severe bone or joint involvement is present some of the complications can justifiably be overlooked and their results accepted. We have pressed the use of streptomycin in patients with considerable cutaneous exfoliation. Occasionally it has had to be stopped and then renewed at lesser dosage. We have not experienced disastrous exfoliative dermatitis. We have had deafness occur in one patient with reduced hearing present in several. Where deafness occurred meningitis had been present, yet recovery was secured. Will anyone contest the acceptance of deafness in a living individual with the certainty of death otherwise? And is not deafness frequently the result of a meningitis in any case? In the cases where reduced hearing gradually occurred similar though less dramatic situation of struggle for life existed. Among the patients where progressive decrease in auditory response was occurring, streptomycin dosage was reduced but its use continued despite such situation. Complications of gastrointestinal nature have bothered us but little. A few days' cessation of the drug and reëstablishment of therapy at a lover level have sufficed to alleviate the condition. The disaster of reactivation of disease due to development of resistant organisms in bone and joint cases, or indeed as related to positive chest conditions present in such cases under treatment, we have not seen. As remarked before, the percentage of permanent closure of sinuses in a consecutive series of cases treated by us with streptomycin far exceeded the percentage of patients who could have been expected to have organisms remaining non-resistant to streptomycin.

Where surgery is employed as commonly as it is in the adequate treatment of bone and joint tuberculosis, all of the complications resulting from similar surgery have been experienced and are factors of failure or factors of delay in recovery. They need no discussion at this point.

And so to close. The foregoing has been based on many facts and many statistics. The reassembling of the facts and the conclusions drawn are, of course, in a large part opinion. Since this is so, disagreement at many points is logically possible. It is certain that all knowledge is not

complete and that as time goes on further data will be secured and the opinions will have to be rearranged again. As a matter of fact it is not impossible that in the near future some agent will be discovered so efficient as to practically wipe out tuberculosis. Then perhaps some newer generation may say, "What were these problems and why the many arguments?" Let us hope this comes quickly and that these terrible lesions may soon be seen no more.



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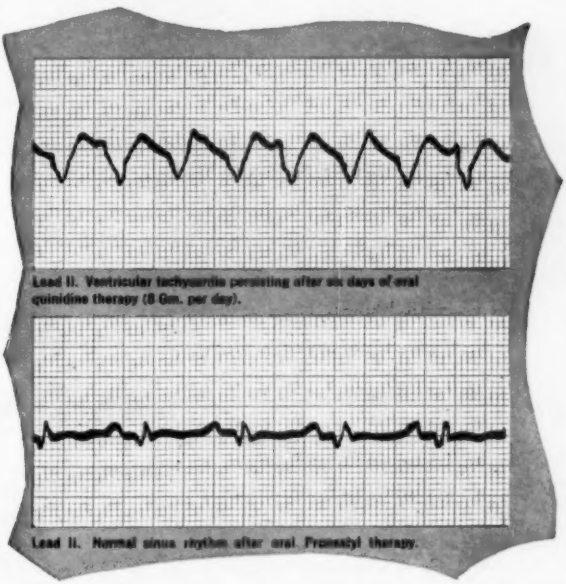

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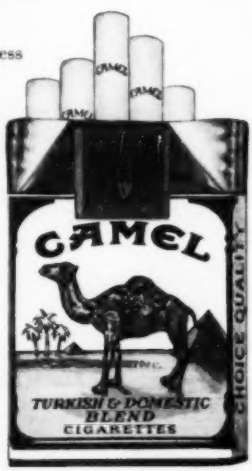

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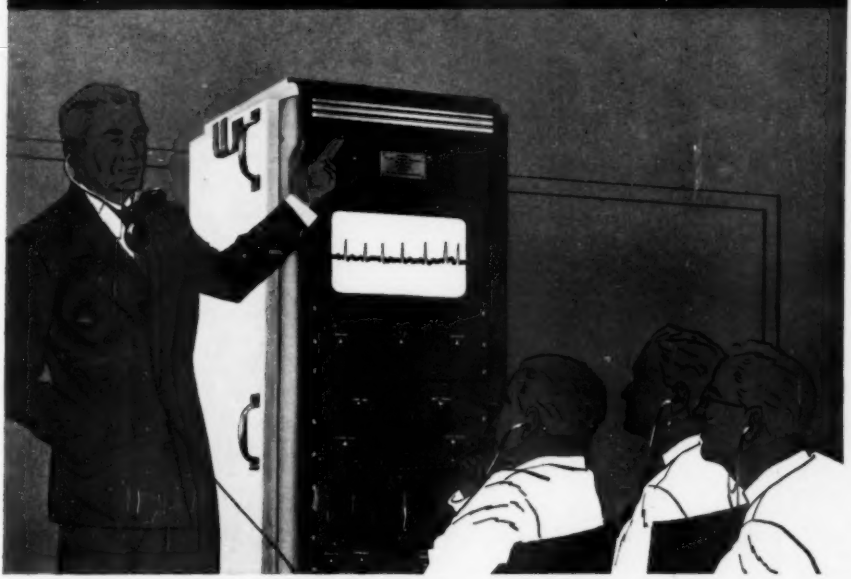

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1. King, F. Q.; Lewis, C. N.; Welch, H.; Clark, E. A., Jr.; Johnson, J. B.; Lyons, J. B.; Scott, R. B., and Cornely, P. B.: J.A.M.A. 143:1 (May 6) 1950.

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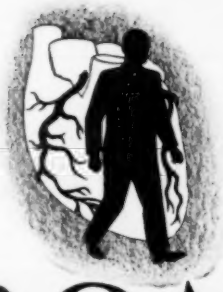

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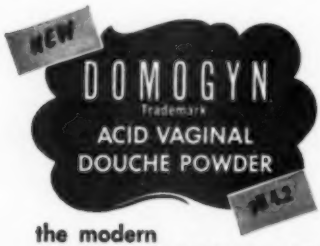

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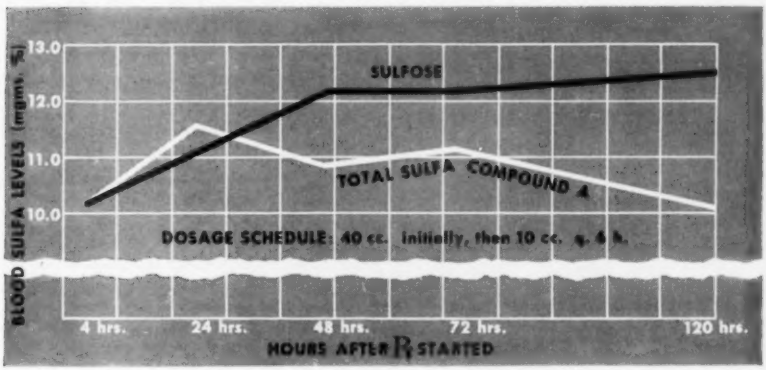

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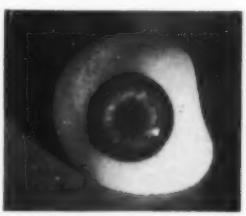

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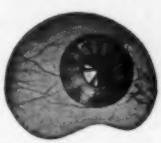

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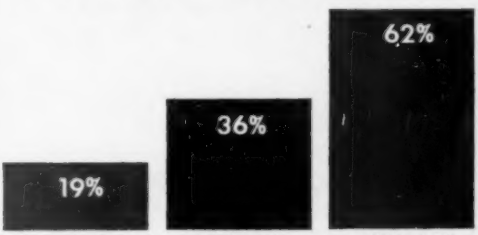

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Nesbit, Reed M. and Lapides, Jack. Observations on Urokon, a New Excretory Pyelographic Medium, University of Michigan Medical Bulletin, 16, 37-42 (1950).

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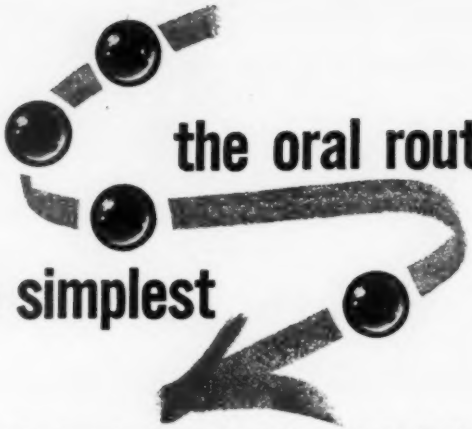

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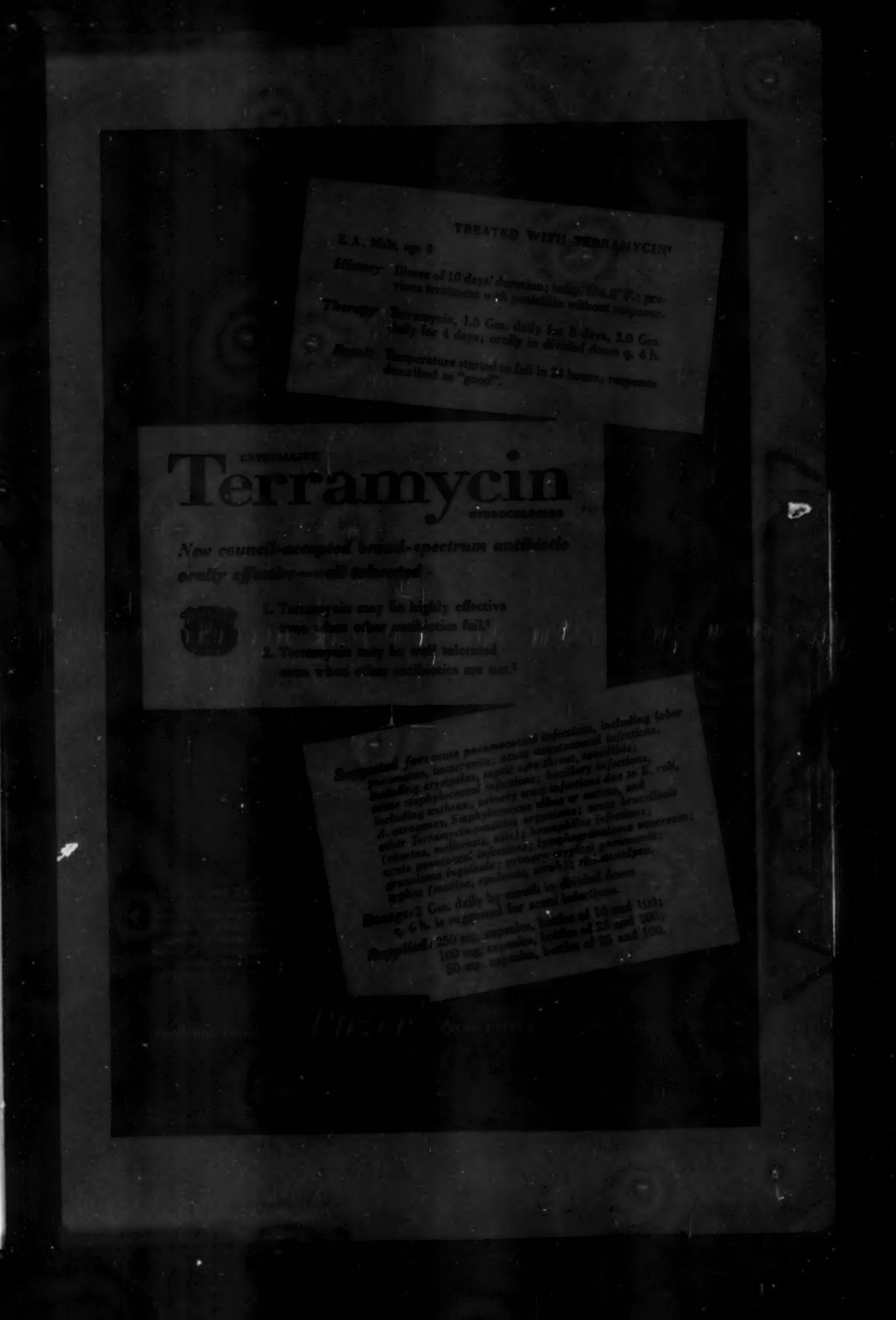
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S.A., Male, age 8
History: Illness of 10 days' duration; today 104.8° F.; previous treatment with penicillin without response.
Therapy: Terramycin, 1.5 Gm. daily for 3 days, 3.0 Gm. daily for 4 days; orally in divided doses q. 6 h.
Result: Temperature started to fall in 24 hours; response described as "good".
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